DISSERTATION
ON

CLINICOPATHOLOGICAL CORRELATION OF NEPHROTIC SYNDROME IN ELDERLY PATIENTS

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CERTIFICATE

This is to certify that this dissertation entitled ***"CLINICOPATHOLOGICAL CORRELATION OF NEPHROTIC SYNDROME IN ELDERLY PATIENTS"*** is the bonafide record of work done by **Dr. K. MUTHUSELVAN**, submitted as partial fulfillment for the requirements of M.D. Degree Examinations, (Branch I) General Medicine, September 2006.

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CONTENTS

INTRODUCTION

INTRODUCTION

Nephrotic syndrome is one of the few modes of clinical expression of renal damage consequent upon an insult by a biological or a non-biological agent resulting in renal injury by differing mechanisms. The diagnosis cannot be complete unless the specific etiology, the mechanism and modes of injury to the kidney and the morphological pattern of response by the kidney to this injury are understood in a given individual. While planning therapy in any form of glomerulonephrtis, one should know about the histopathological nature of the disease. Percutaneous needle biopsy is the best available aid to the clinician in guiding him to know about the nature of the disease.

Before the advent of renal biopsy the knowledge of renal pathology and in general renal disease was gained almost entirely from the autopsy material.

The value of renal biopsy is that the histological pattern

1. Does not change from one form to another except is very limited instances.
2. Provides a dependable guideline to the possible future progression of the renal lesion, thus indicating the prognosis.

3. May indicate the mechanism and mode of injury to the kidney, thus guiding the therapeutic approach.
4. May bring out the etiological agent in some cases.

Unlike other diseases, renal diseases are so complicated that a single lesion may manifest in different ways in different individuals, clinical presentation may vary from patient to patient and this is the reason for much of the misunderstanding in the nature of this group of diseases. This is because, the kidney reacts in a similar way to a number of insults. The terms acute, subacute and chronic glomerulonephritis to describe the clinical presentation do not provide the proper basis for understanding the nature of the renal injury. Renal biopsy and histopathological study are the keys to understand the nature of the renal damage. This is important for both the treatment strategy and prognostication. As said before, since the advent of renal biopsy, there has been a gradual elimination of clinical terms and an attempt instead to achieve histopathological diagnosis based on morphological features present in the glomerulus and various attempts have been made to study clinicopathological correlations in the different types of glomerulopathies in order to establish their significance.

HISTORICAL REVIEW

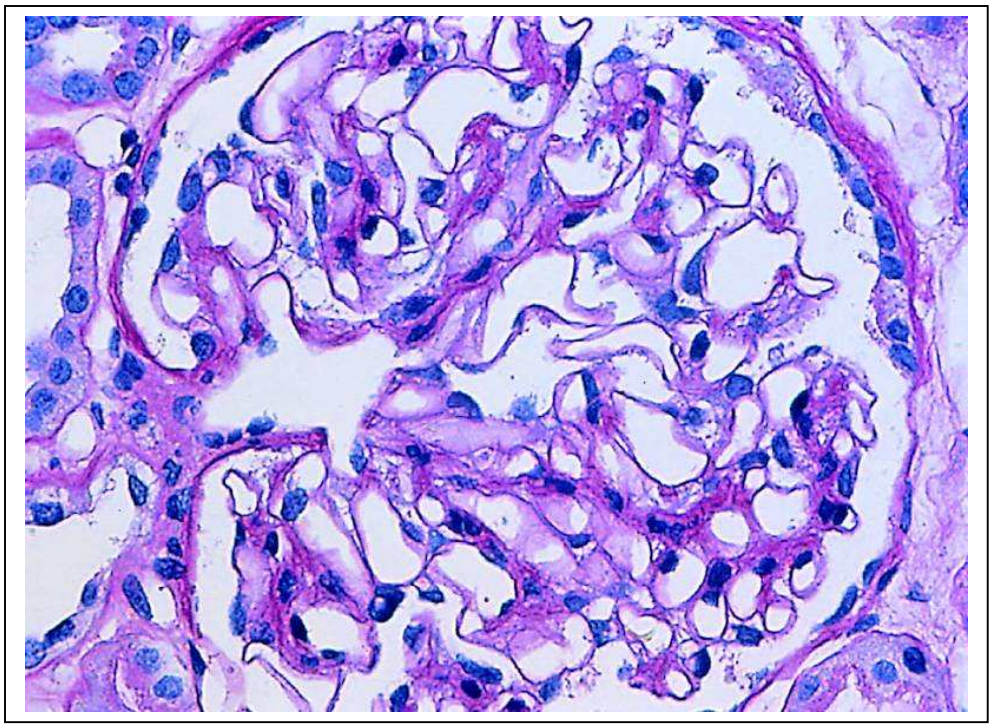
HISTORICAL REVIEW

Cotunnius in the year 1770 was the first to record the association between edema and the presence of coagulable substances in the urine. In 1827 Richard Bright correlated albuminuria and the symptoms of glomerular diseases. In 1917 Epstein suggested that the edema was due to hypoalbuminemia as a result of proteinuria and called as Epstein syndrome.

In 1905 Friiedrich muller introduced the term Nephrosis since the characteristic inflammatory reactive changes of nephritis were not present in the glomeruli of nephrotic patients. In 1908 munk and in 1914 volhard and Fahr observed in patients with edema and albuminuria that renal changes consisted principally of infiltration of the tubules by birefractile lipoid substances. Dunn in 1934 published a paper stating that albuminuria might be due to excessive permeability of glomerular capillaries. Ellis in 1942 called nephrotic syndrome as a type II nephritis. In 1946 Bell, described a group of patients with nephrotic syndrome in whom the glomeruli were not inflamed but the glomerular basement membrane appeared thickened. He seems to have been the first person to use the term membranous glomerulonephritis. Focal glomerulonephritis has long been associated with subacute bacterial endocarditis dating from the classic description of flea bitten kidney by lohlein (1910).

The first renal biopsy was done by Gunta in 1916. In 1929, Dorothy Russel brought out a monogram on renal biopsy. In 1950, Perea reported percutaneous renal biopsy as a safe procedure. This was furthur confirmed by Iverson and Burn in 1951. Its modification in supine position was given by Kark and Muehrcke in 1954. [1] Sarin's publications are among the earliest in our country on percutaneous renal biopsy. In 1968, Pasternack suggested fine needle aspiration cytology of the kidney in the diagnosis of acute rejection. In 1985, Kawamura described open renal biopsy and in 1987 there was modification of Kawamura open renal biopsy forceps.

The precise relationship between serum complement and glomerulonephritis was observed by Kellet in 1935, though the lowered levels of complement in this disease were first discovered by Gunn as early as 1914. The experimental proof that the complement causes renal damage was provided by schwab. The association between low complement and membranoproliferative glomerulonephritis was first noted by West in 1965 and the role of C3 Nephritic factor in complement activation was elucidated by Spitzer in 1969.



NORMAL GLOMERULES

REVIEW OF LITERATURE

NEPHROTIC SYNDROME – REVIEW OF LITERATURE

Nephrotic syndrome is a clinical complex characterised by massive proteinuria, hypoalbuminemia, edema, hyperlipidemia, lipiduria and hypercoagulability. Proteinuria is the key component of this syndrome. The total urinary protein excretion rate in excess of 3.5gm per 1.73m^2 body surface area per day is considered to be in the nephrotic range. Massive proteinuria alone has now come to define the syndrome since this finding reflects serious renal disease whether or not the protein loss lead to hypoalbuminemia, lipid disturbances or edema.

Causes of Nephrotic syndrome:

I Primary Glomerular diseases:

Minimal change disease

Focal and segmental glomerulosclerosis

Membranous glomerulopathy

Membranoproliferative glomerulonephritis - Type I, II , III , other variants

Mesangialproliferative glomerulonephritis

Focal and segmental proliferative glomerulonephritis

II Secondary to other Diseases

(A) Infections

Bacterial	Post streptococcal glomerulonephritis
	Infective endocarditis
	Shunt nephritis
	Leprosy
	Syphilis (congenital and secondary)
	Mycoplasma
	Tuberculosis
	Chronic bacterial pyelonephritis
Viral	Hepatitis – B, C
	Cytomegalovirus
	Epstein Barr virus
	Herpes Zoster
	Vaccinia
	HIV type I
Protozoal	Malaria
	Toxoplasmosis
Helminthic	Schistasomiasis
	Trypanosomiasis
	Filariasis

(B) Neoplasia

Hodgkin's disease

Chronic lymphocytic leukemia

Multiple myeloma

Lymphomas

Carcinomas

Melanoma

Wilm's tumour

(C) Medications

Organic, inorganic elemental mecury

Organic gold

Penicillamine

Street heroin

NSAIDS

Probenecid

Captopril

Lithium

Mephenytoin

Tolbutamide

Chlorpropamide

Rifampicin

γ- interferon

Warfarin

Contrast media

Antivenom

Antitoxin

(D) Multisystem diseases:

Systemic lupus erythematosus

Mixed connective tissue disease

Dermatomyositis

Rheumatoid arthritis

Goodpasture disease

Henoch –Schonlein purpura

Systemic vasculitis

Mixed Cryoglobulinaemia

Takayasu arteritis

Sarcoidosis

Amyloidosis

(E) Heredofamilial and metabolic diseases:

Diabetes mellitus

Hypothyroidism

Grave's disease

Amyloidosis

Alport syndrome

Sickle cell disease

α1 -antitrypsin deficiency

Nail- Petella syndrome

Von Gierke disease

(F) Miscellaneous:

Pre –eclampsia

Renal artery stenosis

Massive obesity

Cyanotic congenital heart disease

Constrictive pericarditis

Severe congestive cardiac failure

Vesico ureteric reflux nephropathy

Kartagener syndrome

Proteinuria:

Proteinuria is the key component of this syndrome and results from altered permeability of glomerular filtration barrier for protein–namely the glomerular basement membrane and the podocytes and their slit diaphragm and perturbation of negative electrostatic charge in glomerular basement membrane barrier. When the glomerular capillary membrane permeability increases by 10 fold the urinary albumin excretion increases 100 fold. The extent of glomerular injury can be assessed by selectivity of proteinuria. A highly selective proteinuria consists almost exclusively of albumin and indicates minimal glomerular damage. A poorly selective proteinuria contains higher molecular weight proteins and indicates a severe renal damage. Larger proteins such as IgM, fibrinogen, $\alpha 1$ and $\alpha 2$ macroglobulin and larger lipoproteins never traverse the glomerular capillary wall and thus are of normal or increased concentration in the plasma.

Hypoalbuminemia:

The hypoalbuminemia is due to excessive urinary losses, increased renal catabolism, excessive gastrointestinal losses, increased trans-capillary escape of albumin and inadequate hepatic synthesis. The availability of drug binding sites may be restricted by hypoalbuminemia which may lead to high levels of free drug enhancing the potential for drug toxicity.

Edema:

Edema of nephrotic syndrome is due to salt and water retention. Hypoalbuminemia reduces the intravascular oncotic pressure that leads to leakage of extracellular fluid from the blood to the interstitium. This reduces the intravascular volume, thereby initiating a series of homeostatic adjustments designed to correct the defect in effective plasma volume. These include activation of renin angiotensin aldosterone system, enhanced vasopressin secretion, stimulation of sympathetic nervous system and suppression of atrial natriuretic peptide release. [2] In some patients, the plasma volume is expanded and renin-angiotensin –aldostetone axis is suppressed suggesting that primary renal salt and water retention also contributes to edema formation. [3] In many instances, edema is a bothersome but not debilitating clinical feature, but occasionally it can be severe and associated with ascites, pleural effusion and pericardial effusion. In the periphery, it is characteristically soft and easily pitting and accumulates in areas of low tissue pressures such as the periorbital areas. It is usually worse about the face upon arising and increases in dependent areas with activity and upright posture.

Hyperlipidemia and lipiduria:

Hyperlipidemia is a frequent accompaniment of the nephrotic state. It is a consequence of both increased hepatic synthesis and decreased catabolism of individual lipid fractions. Decreased plasma oncotic pressure stimulates the hepatic synthesis of apoprotein-B containing lipoproteins. [5,6,7] Depletion of endothelial bound lipoprotein lipase and alteration in the binding capacity of very low density lipoproteins are thought to contribute to the decreased catabolism of lipoproteins. [8] Lowered plasma visocity, reduced oncotic pressure, reduced plasma tonicity, urinary loss of liporegulatory substances and decreased lipoprotein lipase activity may all play a role in the genesis of hyperlipidemia. Total plasma cholesterol and low density lipoproteins are increased in the majority of patients, whereas very low density lipoproteins and triglycerides tend to rise in patients with severe diseases. [5] Lipiduria is a sign of disordered lipid metabolism and is due to excessive filtration of low molecular weight high density lipoprotein.

Hypercoagulability:

This is probably multifactorial in origin and is a consequence of hyperfibrinogenemia, increased in vitro platelet hyperaggregability, increased fibrinogen-to- fibrin transition, altered level and activity of protein C and S, decreased levels of antithrombin III and decreased fibrinolysis. [10,11]

These abnormalities may result in venous and arterial thrombi. Low antithrombin III level in nephrotic patients may not only be due to urinary loss but also to intravascular consumption. Steroid administration alters the level of certain coagulation factors and may provide another stimulus to procoagulant activity. Increased platelet aggregability, increased levels of Von Willebrand factor and β-thromboglobulin promote procoagulant activity. The cause of enhanced platelet aggregability is most likely multifactorial, with hypoalbuminemia, hyperlipidemia and hyperfibrinogenemia all palying a role. [13]

The patients can develop spontaneous peripheral arterial and venous thrombosis, renal vein thrombosis and pulmonary embolism. Acute renal vein thrombosis is characterised clinically by sudden onset of flank/abdominal pain, gross hematuria, left sided varicocele, increased proteinuria and acute decline in glomerular filtration rate. Chronic renal vein thrombosis is usually asymptomatic. Renal vein thrombosis is common in patients with nephrotic syndrome due to membranous glomerulopathy, membranoproliferative glomerulonephritis and amyloidosis. [14]

Functional Consequence of Urinary loss of plasma proteins:

In addition to hypoalbuminemia, hormone binding proteins are typically lost in the urine resulting in several endocrine and metabolic abnormalities. Urinary loss of thyroid binding globulins and thyroxine T_4 results in a low T_4 (both free and bound) and total T_3 level is reduced due to decreased binding to thyroid binding globulins. Total reverse T_3 level is normal but free reverse T_3 is elevated. [15] These changes are associated with hypothyroidism in neptrotic patients. Although most of them remain clinically euthyroid, free T_4 level and TSH level are the best markers for the status of thyroid function.

Hypocalcemia and secondary hyperparathyroidism can occur as a consequence of Vit D deficiency due to increased urinary excretion of cholecalciferol- binding protein and also to low serum concentration of total 1,25 dihydroxy cholecalciferol. [16]

The patients with nephrotic syndrome have increased susceptibility to infection due to loss of immunoglobulin in urine and defects in complement cascade. Peritonitis is caused by either Gram-negative (or) Gram-positive organism and remains a serious complication of the nephrotic syndrome.

Complications of Nephrotic Syndrome:

1. Increased susceptibility to infections.
2. Thrombosis and thromboembolism.
3. Hyperlipidemia and Premature coronany atherosclerosis and increased incidence of myocardial infarction.
4. Protein malnutrition.
5. Iron- resistant microcytic hypochromic anemia.
6. Hypocalcemia and secondary hyperparathyroidism.
7. Hypothyoidism.
8. Unpredictable drug pharmacokinetics and drug toxicity.
9. Acute renal failure.

Infections:

A number of immunological abnormalities have been documented in patients with nephrotic syndrome. These include depressed immunoglobulin levels due to urinary loss, impaired antibody production, defective opsonization due to depressed levels of complement factor B and abnormalities of cellmediated immunity. Non-specific depression of immune response may occur because of malnutrition and vitamin D deficiency or immunosuppressive therapy. These abnormalities may result in increased susceptibility to infection. The peritoneum and lungs are the sites most commonly involved.

Primary peritonitis is particularly characteristic of nephrotic children. The microorganisms commonly involved in peritonitis are Streptococcus pneumoniae, β-hemolytic streptococcus, Hemophilus influenzae and also Gram-negative bacteria.

Cellulitis is also characteristic in severely edematous nephrotics. This arises from skin punctures either spontaneously or as a result of venepuncture. The microorganism responsible include β-haemolytic streptococci and a variety of Gram-negative bacteria.

Thrombosis and Thromboembolism:

This is mainly due to hypercoagulability in nephrotic patients. The patients can develop spontaneous peripheral arterial and venous thrombosis, renal vein thrombosis and pulmonary embolism. Acute renal vein thrombosis is characterised clinically by sudden onset of flank/abdominal pain, gross hematuria, left sided varicocele, increased proteinuria and acute decline in glomerular filtration rate. Chronic renal vein thrombosis is usually asymptomatic. Renal vein thrombosis is common in patients with nephrotic syndrome due to membranous glomerulopathy, membranoproliferative glomenlonephritis and amyloidosis.

20% of adult nephrotic patients develop thromboembolic manifestation. Arterial thrombosis is less frequent than venous thrombosis and occurs mainly in pulmonary, femoral, mesenteric and coronary arteries.

Abnormal calcium homeostasis:

Hypocalcemia and secondary hyperparathyroidism in nephrotic patients are due to reduced intestinal absorption of calcium and blunted calcemic response to parathyroid hormone. Levels of 25-hydroxy cholecalciferol is reduced in nephrotic patients due to loss of this metabolite in urine bound to its vitamin D carrier protein. [16] Severe bone demineralization and bone resorption occurs only in patients with renal insufficiency.

Anemia:

Iron-resistant microcytic hypochromic anemia in nephrotic patients is due to urinary loss of transferrin and decreased level of erythropoietin.

Protein malnutrition:

This is due to proteinuria, tubular catabolism and inadequate compensation by liver.

Treatment of Nephrotic syndrome:

This involves 1. Specific treatment of underlying morphologic entity and if possible causative disease. 2. General measures to control proteinuria if remission is not achieved through immuno suppressive therapy and other specific measures 3. General measures to control nephrotic complications.

Proteinuria:

Non-specific measures:

1. Angiotensin converting enzyme inhibitors.
2. Angiotensin receptor blockers.
3. Nonsteroidal antiinflammatory drugs.

Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers reduce the proteinuria and slow the rate of progression of renal failure by lowering intraglomerular pressure and preventing the development of hemodynamically mediated focal segmental glomerulosclerosis. These drugs are renoprotective in diabetic nephropathy and many other proteinuric glomerulopathies including secondary focal segmental glomerulosclerosis. The antiproteinuric effect of angiotensin converting enzyme inhibitors is dose dependent and independent of changes in systemic blood pressure and also appears to depend on sodium restriction.

Nonsteroidal antiinflammatory drugs also reduce proteinuria by altering glomerular hemodynamics and glomerular basement membrane permeability, due to inhibition of renal prostaglandin synthesis. The beneficial effect of these drugs occurs more rapidly than that of Angiotensin converting enzyme inhibitors, but they are associated with number of adverse effects like hyperkalemia, renal failure and salt and water retention.

EDEMA:

The edema should be managed by moderate salt restriction usually 1-2 gm /day and judicious use of diuretics. Complete resolution of edema is not only unattainable but also undesirable because of risk of volume depetion. In case of mild edema, dietary salt restriction alone is enough. The compliance with sodium restriction can be ascertained by measuring 24 hours urinary sodium excretion. Patients weight should be taken daily. Mild diuretics including thiazide may be sufficient in patients with mild edema. Potassium-sparing diuretics like spironolactone are useful in those patients in whom hypokalemia becomes a clinical problem. Loop diuretics like furosemide are typically used for moderate to severe nephrotic edema. Metalazone may be effective when used alone or in combination with loop diuretics, in patients with refractory nephrotic edema.

In patients treated with diuretics, profound volume depletion may occur that leads to peripheral vasoconstriction, tachycardia, orthostaic hypotension, oliguria, and renal insufficiency. This needs rehydration and cessation of diuretics.

Albumin infusions that increase the plasma volume, are most useful in patients with profound volume depletion. [4] But they are usually excreted within 48hrs. and may also result in pulmonary edema. In extreme cases with marked edema, especially with pulmonary edema in the setting of reduced glomerular filtration rate, intermittent continuous extracorporeal dialysis is useful.

Hyperlipidemia:

Lipid lowering drugs prevent the accelerated atherosclerosis and possibly slow the progression of renal insufficiency and decrease the incidence of myocardial infarctions.

The drugs most commonly used are HMG COA reductase inhibitors and bile acid sequestrants like cholestyramine and colestipol. HMG COA reductase inhibitors reduce the total and LDL cholesterol levels by 10-45% coupled with reduction in triglyceride levels. [9] Bile acid sequestrants lower the total cholesterol levels by upto 30%. Fibric acid derivatives like gemfibrozil, clofibrate lower cholesterol by 10-30% and also lower plasma triglycerides and may raise HDL level but they are associated with increased risk of myopathy. At present, HMG COA inhibitors are the treatment of choice.

Intake of vegetable diet rich in polyunsaturated fatty acids reduces the lipid level by 25-30%.

Hypocalemia:

Oral vitamin D therapy should be given for patients with evidence of osteomalacia or secondary hyperparathyroidism, patients with persistently low serum ionized calcium levels, patients in whom progressive renal insufficiency is anticipated, and patients who have unremitting or frequently relapsing nephrotic syndrome. [17]

Serum calcium levels should be monitored closely in patients on vitamin D replacement therapy. Measurement of bone mineral density should be considered in patients with persistent nephrotic syndrome, particulary if they have received high doses of corticosteroids or have additional risk factors for osteoporosis.

Thromboembolism:

Patients with a history of thromboembolism prior to the onset of nephrotic syndrome should receive prophylactic anticoagulation if they are immobilized or have other major risk factors for clotting. In patients who experience an episode of thrombus or embolus, anticoagulants should be continued for as long as the nephrotic state persists. Intravenous heparin followed by warfarin is the standard treatment for acute renal vein thrombosis. [11,14] International normalized ratio must be carefully monitored during the anticoagulation therapy. Prolonged immobilization and volume depletion should be avoided.

Infection:

The patient should be treated with intravenous broad spectrum antibiotics covering both Gram-positive and Gram-negative organism. Prophylatic use of antibiotics, pneumococcal vaccine, or intravenous administration of hyperimmune globulin should be considered in high-risk cases. Vaccination should be given whenever possible during periods of remission, as nephrotic syndrome may impair the antibody response to vaccination. Pneumococcal vaccination is still recommended for children over 2 years of age and for adults with severely depressed immunoglobulins, particularly if nephrotic syndrome is likely to be persistent or if renal failure supervenes.

Minimal Change disease:

Minimal change disease is the most common cause of the nephrotic syndrome in children and is not uncommon in adults. The clinical presentation is similar in old and young but older individuals are much more likely to have nonselective proteinuria, microscopic hematuria, hypertension and renal insufficiency. [22,26] Classically the disease appears soon after a viral respiratory tract infection.

Pathology:

There are no changes on light microscopy (or) only slight membrane thickening and mesangial proliferation. There are no immune deposits but findings of mesangial hypercellularity and sparse deposits of C3 and IgM portend a worse prognosis. [18] Electron microscopy reveals characteristic diffuse effacement of foot process of visceral epithelial cells. (foot process fusion).

Treatment:

This disease is highly responsive to steroids and carries an excellent prognosis. Spontaneous remission occurs in 30-40% of childhood cases but is less common in adults. Adult patients have to be treated with oral prednisolone 1-1.5mg/kg body weight per day for 4 weeks followed by 1mg/kg per day on alternative days for 4 weeks. The steroid dependent and frequently relapsing patients should be treated with cyclophosphamide 2-3mg/kg per day or chlorambucil 0.1-0.2mg/kg per day after steroid induced remission and continued for 8-12 weeks. Lorca and ponticelli reported that 80% of patients with minimal change disease responded initially to steroids or cytotoxic agents, almost a third experienced relapse and half of them developed renal failure or died, and they recommended treating the patient initially with corticosteroids followed by a cytotoxic agent for 12 weeks if steroids are not tolerated or are ineffective.

Membranous Nephropathy:

Membranous nephropathy is the most common cause of nephrotic syndrome in the elderly. At least 85% of patients with membranous nephropathy present with nephrotic proteinuria. The most common causes of secondary membranous nephropathy in elderly are drugs like nonsteroidal anti-inflammatory drugs and cancer.

Brown reported that 11% of patients with membranous nephropathy had an underlying malignancy. [21] Males are affected twice as frequently as females.

Clinical Features:

70-80% of patients presenting with hypoalbuminemia, hyperlipidemia, peripheral edema and lipiduria. Hypertension occurs in 13 to 55% of cases and microscopic hematuria occurs in 70 –80% of cases. 4-52% of patients have renal vein thrombosis. Complete spontaneous remission occurs 20-40% of cases. Older patients are more susceptible to the extra renal complications of nephrtoic syndrome and its treatment. [22]

Pathology

Electron Microscopy:

Presence of subepithelial immune complex deposits or their structural consequences.

Four ultrastructural stages of membranous glomerulopathy have been described by Ehrenreich and Churg. [19]

Stage I – This is characterized by the presence of scattered or more regularly distributed small immune complex –type electron dense deposits in subepithelial zone between the basement membrane and epithelial cells.

Stage II – This is characterized by projections of basement membrane materials around the subepithelial deposits.

Stage III – New basement membrane material surrounds the deposits and thus in cross section, there is basement membrane material between the deposits and the epithelial cytoplasm.

Stage IV – This is characterized by loss of the electron density of the deposits, often resulting in irregular electron lucent zones within an irregularly thickened basement membrane.

Stage V – This is characterized by a repaired outer basement membrane zone with only residual basement membrane disturbances in the inner aspect of the basement membrane. Mesangial dense deposits are rare in idiopathic membranous glomerulopathy but frequent in secondary membranous glomerulopathy.

Light Microscopy:

Diffuse global granular capillary wall thickening in the absence of significant glomerular hypercellularity. Stage I lesions may not be discernible by light microscopy but stage II, III, IV lesions readily discernible.

Immuno fluorescence microscopy:

Diffuse global granular capillary wall staining for Ig and complement, most frequently Ig G and C3.

Treatment:

Spontaneous and complete remission occurs in 40% of the patients. Repeated relapses and remission without worsening of renal function occurs in 30-40%. 10-20% of the patients suffer a slow progressive decline in glomerular filtration rate that typically culminate in end stage renal disease after 10-15 years. In patients with proteinuria less than 3.5 gm/day, the risk of progression is low. The patients should be closely monitored with a low-salt diet, strict blood pressure control and angiotensin converting enzyme inhibitor for reduction of proteinuria. The patients with proteinuria of 3.5-8 gm/day but normal renal function are at medium risk and they should follow the above suggestion and can be treated by immunosuppressive regimens with corticosteroids and chlorambucil or cyclophosphamide for 6 months. The highest risk patients-those with more than 8gm/day of proteinuria and renal dysfunction must be treated with corticosteroids and cytotoxic agents. Renal transplantation is a successful treatment option for patients with end stage renal disease.

Membranoproliferative Glomerulonephritis:

Membranoproliferative glomerulonephritis are usually seen in children between the age of 8-16 years and nearly in an equal proportion of males and females. Membranoproliferative glomerulonephritis appears to be decreasing in frequently.

Clinical Features:

Half of the patients present with all the components of the nephrotic syndrome and 25% of patients present with a combination of asymptomatic hematuria and asymptomatic proteinuria. 25-30% of patients have hypertension and renal dysfunction occurs in at least half of the cases.

Pathology:

Electron Microscopy:

Type I – Mesangial interposition into an expanded subendothelial zone that contains electron –dense immune complex deposits is the ultrastructural hallmark of this type. [23] New basement membrane material is formed around the subendothelial deposits and around the projection of mesangial cytoplasm.

Type II – Dense –deposit disease. Development of discontinuous electron dense bands within glomerular basement membrane is the pathognomonic of this type. This is accompanied by spherical to irregular mesangial dense deposits and occasionally subendothelial and subepithelial deposits.

Light Microscopy:

Type I – Most common histologic feature of this type are diffuse global capillary wall thickening and endocapillary hypercellularity. [23] Infiltrating mononuclear leukocytes and neutrophils also contribute to the glomerular hypercellularity. The consolidation of glomerular segments that results from these changes often causes an accentuation of the segmentation. (hypersegmentation or lobulation). The distinctive feature of this type is doubling or more complex replication of glomerular basement membrane.

Type II – The light microscopic appearance does not always have membranoproliferative appearance and can mimic other types of glomerulonephritis. Spontaneous remission is uncommon and steroids may delay the progression of disease. The course of disease is progressive. Prognosis is worse for Type II disease than for Type I, because of frequent association with crescentic glomerulonephritis and chronic tubulointerstitial nephritis. Poor prognostic factors in idiopathic membranoproliferative glomerulonephritis type I include hypertension, impaired glomerular filtration rate, nephrotic rather than non-nephrotic disease, cellular crescents on biopsy.

Mesangioproliferative – glomerulonephritis:

In 5-10 % patients with idiopathic nephrotic syndrome, renal biopsy reveals a diffuse increase in glomerular cellularity predominantly due to proliferation of mesangial and endothelial cells and infiltration by monocytes. Immuno fluorescence microscopy shows deposits of Ig A, IgG, IgM and/or complement (or) absence of immuno reactants. This morphological entity is a heterogenous group of disease that include a typical forms of minimal change disease and focal segmental glomerulosclerosis and resolving forms of immune complex and pauci-immune glomerulopathy. In keeping with the heterogeneity of this diagnosis, the prognosis is variable. Persistent nephrotic range proteinuria and renal insufficiency signals a poor prognosis with many patients progressing to end stage renal disease over 10-20 years despite immuno suppressive therapy.

Focal Segmental glomerulosclerosis:

This pattern has been reported in 7% of renal biopsies of elderly nephrotic patients. Juxtamedullary glomeruli are frequently affected with positive immunofluorescence for IgM and C3 complement. focal segmental glomerulosclerosis is seen often as an end result of other glomerulopathies and secondary to advanced systemic diseases like hypertension and diabetes mellitus. [24] Clinically this is characterised by varying degree of proteinuria from non-nephrotic to nephrotic which is hallmark of the focal segmental glomerulosclerosis.

Haematuria occurs in 50% of patients and 30% of patients present with some degree of renal insufficientcy and 30% of cases are hypertensive which is more in adults. The patients with perihilar focal segmental glomerulosclerosis accompanied by glomerular hypertrophy, have more commonly non-nephrotic range proteinuria than the patients who do not have glomerular hypertrophy. The patients with collapsing variant often have more selective proteinuria and renal insufficiency but less hypertension than the typical variant. The patients with glomerular tip lesion variant often present with rapid onset of edema similar to minimal change glomerulopathy. High dose oral prednisolone 1-1.5mg/kg/day for 2-3months followed by a slow steroid taper can induce remission in over half of the patients.

Multiple Myeloma:

Almost 50% of patients have overt renal insufficiency at sometime during the course of the disease and renal disease may be the first indicator of multiple myeloma. The commonest clinical manifestation is detection of light chain/ Bence-Jones proterinuria, observed in 65-100% of patients. Intratubular obstruction by myeloma protein may result in acute renal failure and is not always reversible. Hypertension and hematuria are rare. Renal histology shows dilated tubules containing fractured glassy eosinophilic casts surrounded by multinucleated giant cells and widespread tubular atrophy, interstitial fibrosis and inflammation.

On immunofluorescence, the cast shows light chains besides immunoglobulins, Tamm-Horsfall protein and complement. Secondary amyloidosis occurs in 6-15% of patients. The patients have to be treated with adequate hydration, vigorous control of hypercalcemia and hyperuricemia and cautious use of potentially nephrotoxic agents. Patients with severe renal failure are treated with peritoneal dialysis or plasmaparesis. Survival rate on maintanance dialysis is about 50% at 1 year. Renal transplantation should be done, only after chemotherapy induced prolonged remission and control of tumour growth.

Renal Amyloidosis:

Amyloidosis is characterised by deposition of amyloid fibrils in glomenular capillary loops. In primary amyloidosis, these fibrils are light chains that have a composition similar to those of Bence Jones proteins. Patients with plasma cell dyscrasias often have an amyloidosis similar to that seen with primary amyloidosis. Secondary amyloidosis is associated with chronic inflammatory diseases such as infections and inflammatory bowel diseases. Glomeruli are involved in 75-90% patients usually in association with involvement of other organs. The clinical correlate of glomerular amyloid deposition is nephrotic –range proteinuria and >50% of patients having oliguria and 20-25% presenting with hypertension.

Renal failure in amyloidosis is due to amyloid deposition in renal vasculature, Fanconi's syndrome, nephrogenic diabetes insipidus (or) renal tubular acidosis due to involvement of tubular interstitium. Rectal biopsy and abdominal fat pad biopsy reveal amyloid deposits in about 70% of patients and may obviate the need for renal biopsy.

Earliest pathological changes are mesangial expansion by amorphous hyaline material and thickening of the glomerular basement membrance and later developed large number of nodular eosinophilic masses. With Gongo Red stain, deposits show apple green birefriengence under polarised light and electron microscopy reveals characteristic non-branching extra cellular amyloid fibrils. Tubulointerstitial and vascular deposits of amyloid are also seen. The patients with primary amyloidosis progress to end stage renal disease in average of 2-3 years. Melphalon and prednisone can reduce proteinuria and improved renal function in some patients. Colchicine delays the onset of nephropathy. Remission may be achieved in secondary amyloidosis by eradication of the underlying cause. Renal transplantation is a viable option in patients with secondary amyloidosis whose primary diseases has been eradicated. Most of the death is due to infections and cardiovascular complications. Recurrence in the allograft is common but rarely leads to graft loss.

AIMS OF THE STUDY

AIMS OF THE STUDY

1. To study the clinical profile, biochemical alteration in renal function and histopathological appearance in renal biopsy in 25 cases of nephrotic syndrome in elderly patients.

2. To diagnose the etiology.

3. To correlate the histopathological appearance with the clinical features and biochemical findings.

MATERIALS AND METHODS

MATERIALS AND METHODS

To predict the prognosis and the line of management in a patient with nephrotic syndrome, we depend upon the histopathological examination of renal tissue. So the renal biopsy forms the corner stone in the line of management of any patient with nephrotic syndrome. The percutaneous renal biopsy if performed by a well trained person, has a low complication rate. Some patients may not be willing to subject themselves to this procedure. In this study, the renal biopsy was carried out without ultrasound guidance. The ultrasound guided biopsy gives better results.

Selection Criteria:

1. The patients with clinical features suggestive of nephrotic syndrome were included.
2. The patients above the age of 50 years and of both sexes were included.
3. The patients having nephrotic range proteinuria only were included.

Period of the study:

From December 2003 to July 2005.

No. of cases studied: 25

All patients who were admitted in the medical wards and in the nephrology ward of Thanjavur Medical College Hospital from December 2003 to July 2005 with clinical features suggestive of nephrotic syndrome were taken up for this study. The patients above the age of 50 years and both sexes were included. The patients were included in this study only when the proteinuria was in the nephrotic range.

The methods of examination included are

1. Clinical Examination.
2. Urine Examination.
3. Biochemical Examination.
4. Histopathological Examination.

Urine Examination:

1. Albumin by heat coagulation method.
2. Sugar by Benedict's method.
3. Deposits for red blood cells, various casts & cells.
4. 24 hours urine protein estimation.
5. Urine culture in selected cases.
6. Urine Bence-Jones protein in selected cases.

Bio chemical Examination:

1. Blood sugar.
2. Blood urea.
3. Serum creatinine.
4. Serum electrolytes.
5. Serum Cholesterol.
6. Serum total protein.
7. Serum electrophoresis in selected cases.

Plain X-ray Abdomen KUB was taken in all patients to locate the site of kidney to be biopsied. An abdominal ultrasound was done in all patients to assess the kidney size and to rule out other structural abnormalities. Before renal biopsy, the coagulation profile like bleeding time, clotting time, and blood grouping was done for all patients and haematological disorders were ruled out and two units of blood were reserved. Informed consent was obtained from the patients before renal biopsy.

Procedure:

Three types of needles can be used for renal biopsy

1. Inversum and Brun.
2. Franklin's Modification of VIM Silverman needle.
3. TRU- CUT needle.

In this study 'TRU –CUT –NEEDLE' was used.

Techique of Renal Biopsy:

The patient is placed prone, straight and flat on his belly with a sand bag between the costal margin and the iliac crest. After the patient is positioned the kidney can be marked on the back of the patient. The skin is prepared by cleaning with cetavlon and betadine solution. A small area of skin around the skin mark is anaesthetized by 2% xylocaine infiltration.

A small incision about 2-3mm is made at the point of biopsy with No.11 B.P scalpel blade. The depth of the kidney from the skin surface is assessed by inserting a disposable lumbar puncture needle. As the patient holds the breath, the needle is advanced. It will encounter resistance of the subcutaneous tissue, paraspinal muscles and renal capsule in succession. As soon as the capsule is pierced a ‘give’ is felt. The patient is asked to breathe freely. The needle will show a forward and backward movement. The lumbar puncture needle is withdrawn and the depth was noted. This is marked on the biopsy needle.

The patient is asked to hold his breath once again. The biopsy needle is advanced to the desired depth. The needle is left in position and the patient is asked to breathe. The needle will execute movement. The patient is told to hold his breath again and the biopsy is done. Two bits are taken –one superficial and one deep to ensure that the cortico-medulary region is included in the biopsy.

The diseases such as focal glomerulosclerosis in which the lesion commences in the juxta medullary region will not be missed. The whole assembly is withdrawn. The renal tissue is preserved in saline and the material is sent for histopathological examination.

Tincture benzoin seal with a thick pad of gauze is secured at the biopsied site. The patient lies still in bed for a few hours. The patient is observed for haematuria for the next twenty four hours.

Complications

1. Local pain.
2. Microscopic haematuria.
3. Frank haematuria.
4. Tear in kidney.
5. Perirenal hematoma.
6. Infection.
7. Arterio – venous fistula.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

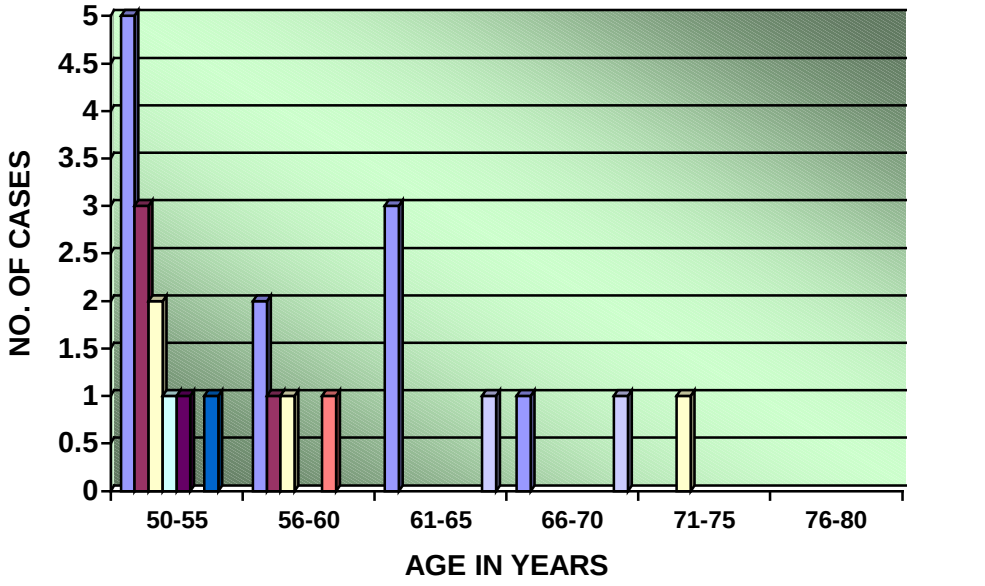
All observations made are recorded in various tables. Totally 25 cases of nephrotic syndrome are studied with renal biopsy.

Table I

AGE INCIDENCE

Pathological lesion	Total No. of Cases	Male	Female	Age in Years					
				50-55	56-60	61-65	66-70	71-75	76-80
Membranous Nephropathy	11	8	3	5	2	3	1	-	-
Membrano Proliferative	4	3	1	3	1	-	-	-	-
Mesangio Proliferative	4	4	0	2	1	-	-	1	-
Focal segmental glamerulo sclerosis	1	0	1	1	-	-	-	-	-
Chronic glomerulonephritis	1	0	1	1	-	-	-	-	-
Acute interstitial nephritis	1	1	0	-	1	-	-	-	-
Multiple myeloma	1	1	0	1	-	-	-	-	-
Amyloidosis	2	1	1	-	-	1	1	-	-

AGE INCIDENCE



The minimum age noted is 51 years, the maximum 71 years of age. Major incidence was noted in the 50-55yrs of age group (52%). The minimum incidence was noted in the 71-75 years of age group (4%).

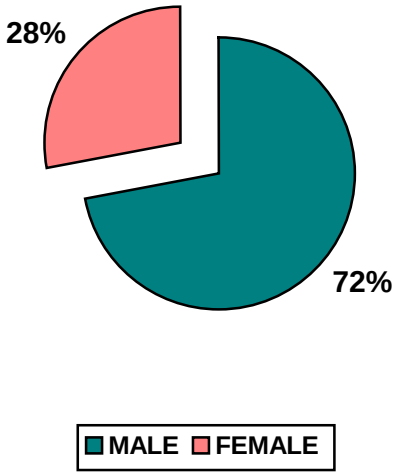
Table II

SEX INCIDENCE

Sex	No. of cases	Percentage
Male	18	72%
Female	7	28%

Sex incidence noted in this study- male to female ratio is 7:3

SEX INCIDENCE



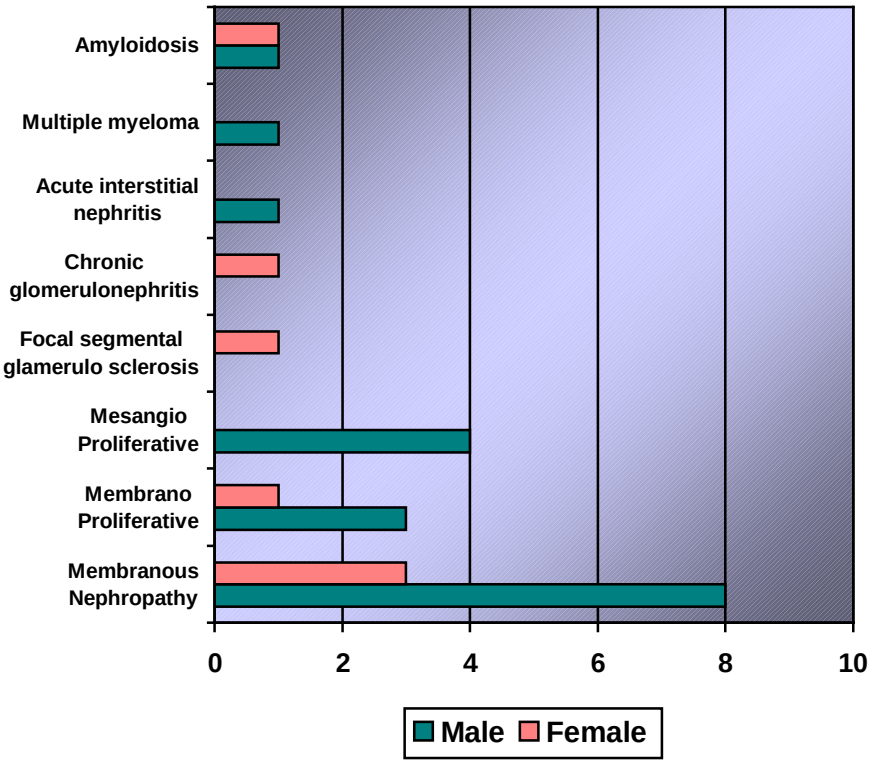


Table III

PRESENTING SIGNS AND SYMPTOMS

Presenting signs & Symptoms	Membranous	Membrano proliferative	Mesangio proliferative	Focal segmental glomerulo sclerosis	Chronic glomerulo nephritis	Acute Interstitial nephritis (Native drug)	Multiple myeloma	Amyloidosis
Mode of Onset								
a) Acute	-	-	-	-	-	1	-	-
b) Gradual	11	4	4	1	1	-	1	2
Anasarca	11	4	4	1	1	1	1	2
Oliguria	5	2	3	-	1	1	-	2
Ascites	4	3	1	-	-	-	-	-
Hypertension	3	1	4	-	-	-	-	-

In all the cases, it was of gradual onset except in native drug ingestion where it was sudden onset. The duration of onset varying between 1 month to 5 months. Anasarca was the major complaint of all the cases(100%). Scanty mictuirition was present in 56% of cases. Ascites was present in 32% of cases. Hypertension was noted in 32% of cases.

PRESENTING SIGNS AND SYMTOMS

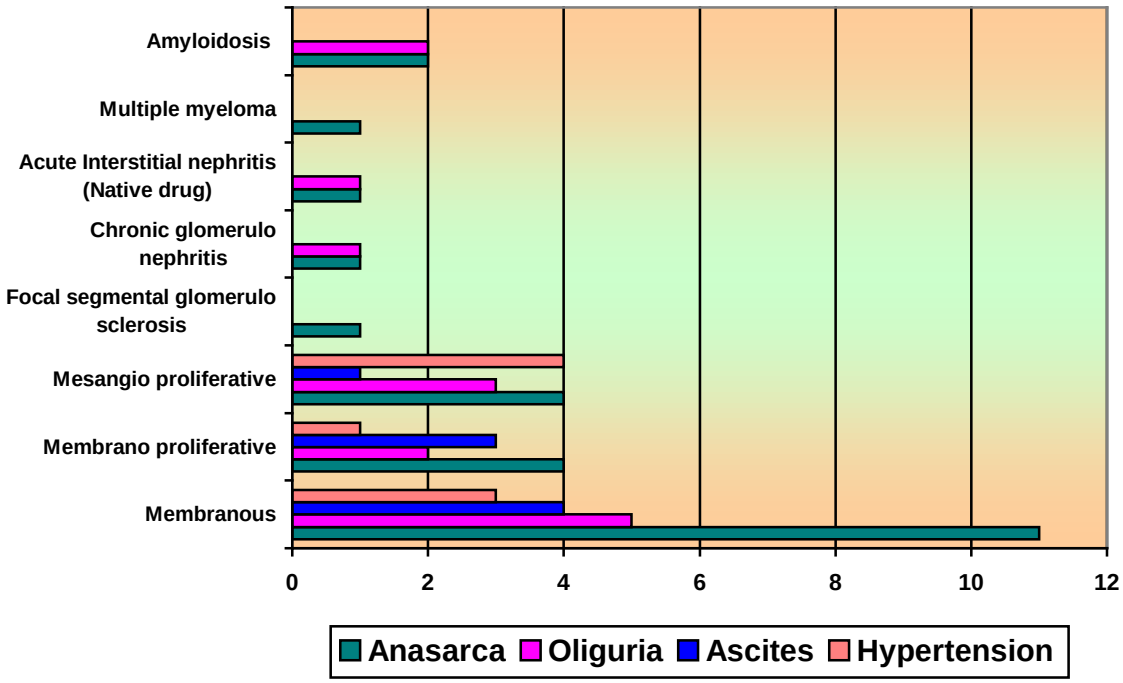
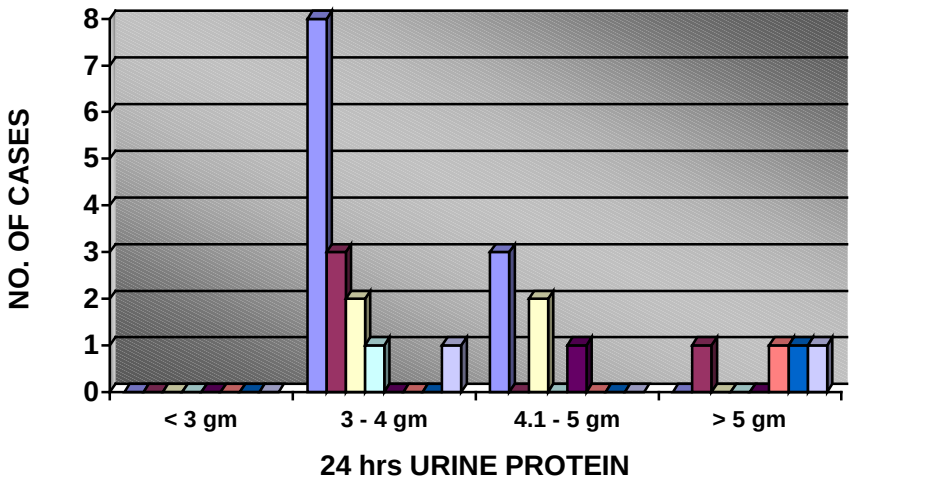


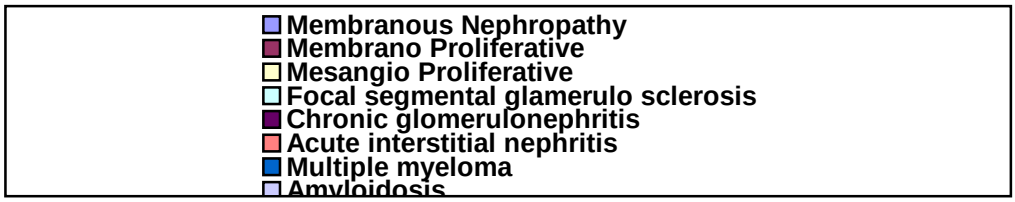
Table IV

URINARY FINDINGS

Urine investigation	Membranous	Membrano proliferative	Mesangio proliferative	Focal segmental glomerulo sclerosis	Chronic glomerulo nephritis	Acute Interstitial nephritis	Multiple myeloma	Amyloidosis
24 hrs urine protein < 3.0gm	-	-	-	-	-	-	-	-
3.0 – 4.0 gm	8	3	2	1	-	-	-	1
4.1 – 5.0 gm	3	-	2	-	1	-	-	-
> 5.0 gm	-	1	-	-	-	1	1	1
Microscopic hematuria < 5 cells / hpf	4	1	-	-	1	-	-	-
5 – 10 cells / hpf	2	1	-	-	-	-	-	-
> 10 cells / hpf	-	-	-	-	-	-	-	-

PROTEINURIA





Nephrotic syndrome was diagnosed on the basis of 24 hours urinary protein excretion per 1.73m2 body surface area per day. In three cases with proteinuria between 3.0 to 3.5gms, the proteinuria was in the nephrotic range when correlated with body surface area.

The average proteinuria noted in the various groups is given in table VI

Membranous Lesion	3.88 gm/24 hours
Membrano Proliferative	4.05 gm/24 hours
Mesangio proliferative	4.04gm/24 hours
Focal segmental glomerulo Sclerosis	3.86 gm /24 hours
Chronic glomerulonephritis	4.20gm/24 hours
Chronic interstitial nephritis (native drug intake)	6.73 gm/24 hours
Multiple myeloma	6.8 gm / 24 hours
Amyloidosis	3.78 gm / 24 hours

Microscopic hematuria was noted in 9 cases (36%)

Table V

BIOCHEMICAL FEATURES

Biochemical investigation	Range	No. of cases	Percentage
Blood urea	< 40 mg%	17	68 %
	> 40 mg%	8	32 %
Serum creatinine	< 1.0 mg%	7	28 %
	1.0 - 2.0 mg%	10	40 %
	> 2.0 mg%	8	32 %
Serum cholesterol	< 200 mg%	-	-
	201 – 300 mg%	15	60 %
	301 – 400 mg%	8	32 %
	401 – 500 mg%	2	8 %
	> 500 mg %	-	-
Serum protein	3.0 – 4.0 gm%	-	-
	4.1 – 5.0 gm%	11	44 %
	5.1 – 6.0 gm%	14	56 %

Blood urea in this study ranged from 24 mg% to 108 mg%. Serum creatinine ranged from 0.8 to 3.8 mg%. Serum cholesterol ranged from 234 mg% to 420mg % and serum proteins ranged from 4.4gm to 5.8gm%. High blood urea and serum creatinine was noted in membranous, membranoproliferative, mesangioproliferative, amyloidosis and multiple myeloma. Serum electrocytes were normal in all the cases.

The average serum proteins, serum cholesterol, blood urea and serum creatinine noted in various groups of lesions is given is Table VI.

Table VI

MAJOR CLINICAL AND BIOCHEMICAL FINDINGS FOR EACH INDIVIDUAL HISTOLOGICAL GROUPS AMONG 25 CASES OF NEPHROTIC SYNDROME

Particulars	Membranous	Membrano proliferative	Mesangio proliferative	Focal segmental glomerulo sclerosis	Chronic glomerulo nephritis	Acute Interstitial nephritis	Multiple myeloma	Amyloidosis
Total No. of cases	11	4	4	1	1	1	1	2
Age in years	59 (52 to 66)	54 (51 to 58)	58 (52 to 71)	55	54	56	55	68
Anasarca	100 %	100 %	100 %	100 %	100 %	100 %	100 %	100 %
Hypertension	12 %	4 %	16 %	-	-	-	-	-
24 hrs urine protein in gms	3.88 (3.31 to 4.66)	4.05 (3.20 to 5.59)	4.04 (3.80 to 4.25)	3.86	4.2	6.73	6.8	3.78
Serum total protein in gm %	5.0 (4.4 to 5.7)	5.4 (4.8 to 5.7)	5.4 (4.8 to 5.8)	5.6	4.8	5.7	5.5	5.6
Serum Cholesterol in mg %	289 (234 to 372)	274 (240 to 286)	370 (310 to 420)	256	380	294	248	300
Blood urea in mg %	43 (28 to 80)	42 (24 to 80)	41 (30-108)	28	30	32	92	63
Serum creatinine in mg %	1.5 (0.8 to 3.8)	1.6 (1.0 to 3.8)	2.4 (1.1 to 3.8)	0.8	1.0	1.0	3.8	2.0

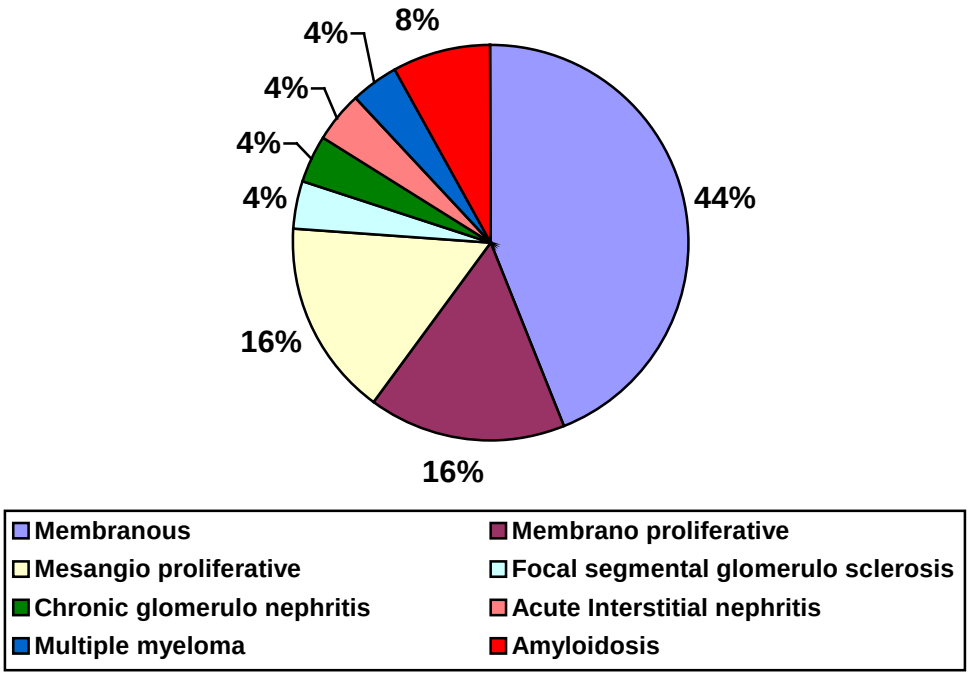
Table VII

AETIOLOGICAL DIAGNOSIS AND HISTOPATHOLOGICAL FEATURES

Pathological diagnosis	No. of cases	Percentage
Membranous Lesion	11	44 %
Membrano Proliferative	4	16 %
Mesangio proliferative	4	16 %
Focal segmental glomerulo Sclerosis	1	4 %
Chronic glomerulonephritis	1	4 %
Acute interstitial nephritis (native drug intake)	1	4 %
Multiple myeloma	1	4 %
Amyloidosis	2	8 %

Majority of the lesions belonged to membranous glomerulopathy (44%). History of native drug ingestion in one case, probably the reason for renal involvement in the form nephrotic syndrome, was noted. 2 cases of amyloidosis secondary to tuberculosis was noted. One case of multiple myeloma producing nephrotic syndrome was also noted.

HISTOPATHOLOGICAL FEATURES



DISCUSSION

DISCUSSION

Nephrotic syndrome may occur due to a number of cases. In this study, out of 25 cases, 20 cases (80%) were due to primary glomerular disorders. One case (4%) of chronic glomerulonephritis, one case (4%) of multiple myeloma, 2 cases (8%) of amyloidosis secondary to tuberculosis and one case (4%) following the ingestion of negative drug presented as nephrotic syndrome were also noted in this study. In this study, among the primary glomerular diseases, membranous lesion was in 44% of cases, membranoproliferative lesion in 16% of cases, mesangioproliferative in 16% of cases, focal segmental glomerulosclerosis in 4% of cases.

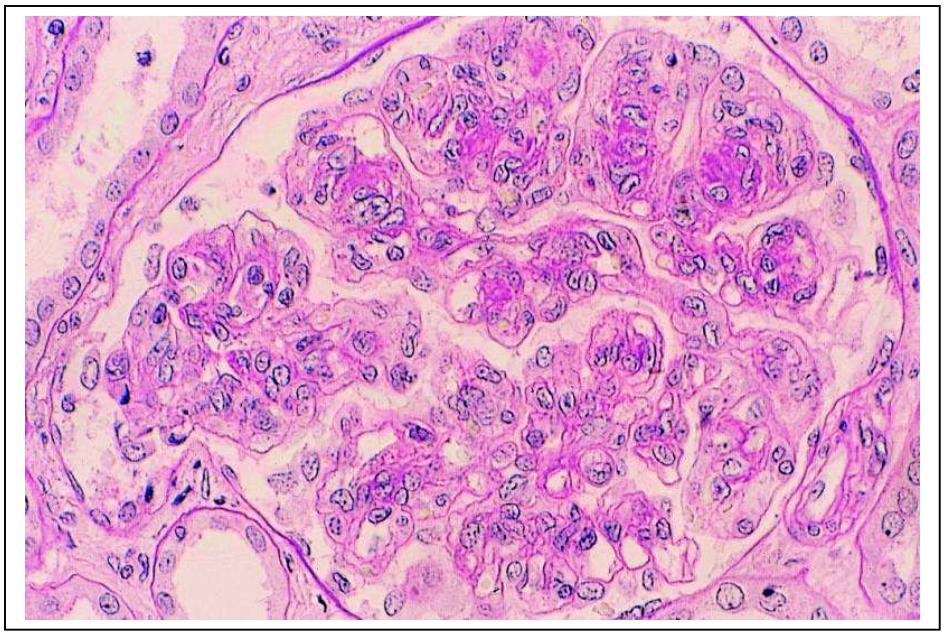
Age Incidence:

Membranous glomerulopathy is unusual in children and adolescents, although it may occur at any age, It has a peek incidence between the ages of 30 to50 years. Membrano profilerative lesion occurs commonly in young adults below the age of 30 years. In mesangioproliferative lesion, any age can be affected but patients are usually older children and young adults. Focal segmental glomerulosclerosis more commonly occurs in younger age groups but has been reported to be present in 7% of renal biopsy of elderly patients with nephrotic syndrome. In case of multiple myeloma the average age group affected is 55yrs (31-77yrs).

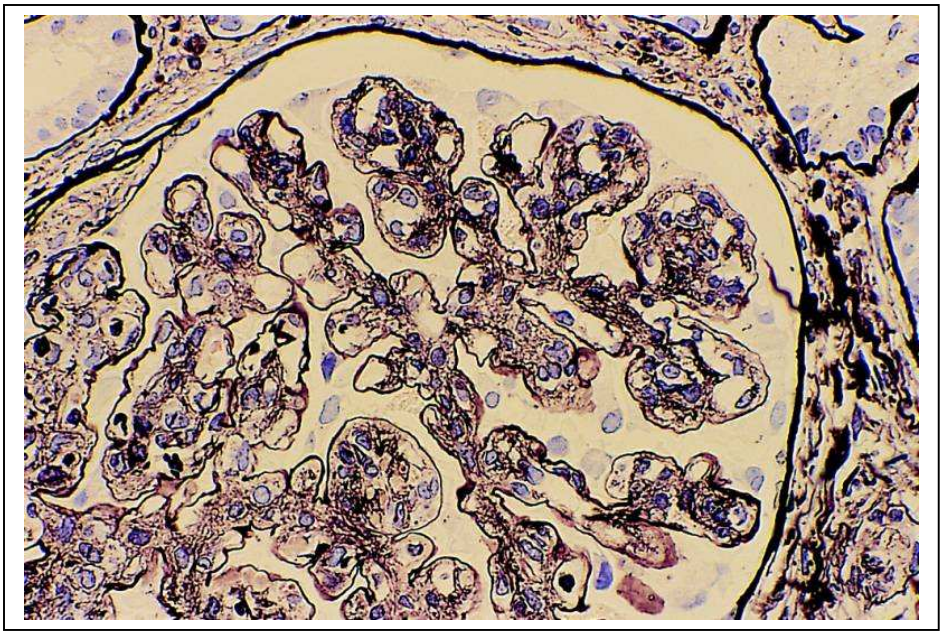
In this study, major incidence was noted in 50-55 years of age (52%) and minimum incidence was noted in 71-75 years of age group (4%). The study of average age incidence in various type of glomerulonephritis revealed that membranous nephropathy in 59 years, membranoproliferative 54 years, masangioprolifertive 58 years, focal segmental glomerulosclerosis 55 years, chronic glomerulonephritis 54 years, acute interstitial nephritis 55 years, amyloidosis 68 years, multiple myeloma 55 years.

Sex incidence:

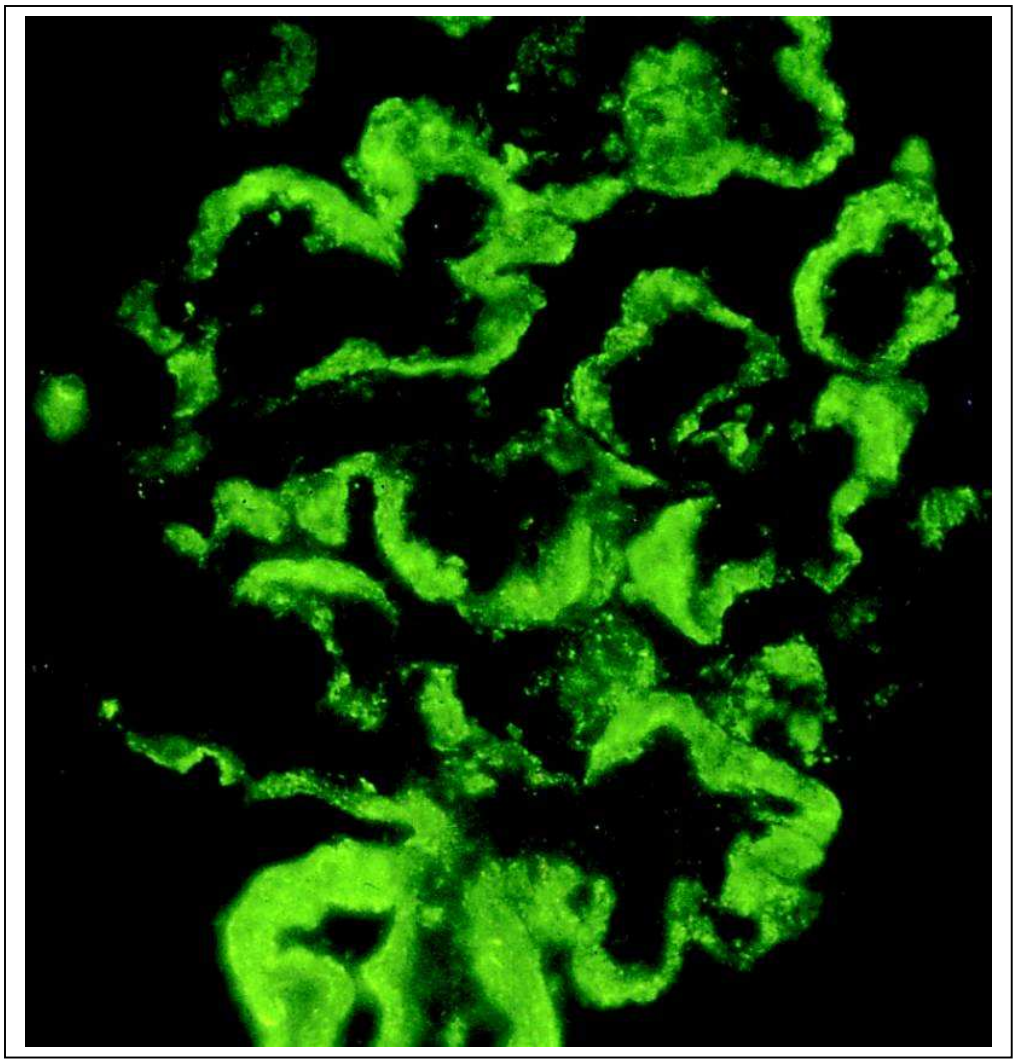
Males outnumbered females in this study. The male : female ratio is 7:3. Various authors like Sharma et al and Hanashetty et al also showed male preponderance. Mukherjee [50] reported a female incidence of 31% whereas Shanbag [49] reported 26.6%. In membranous glomerulopathy, males are affected twice as frequently as females. In membrano proliferative lesion the sex ratio is equal. Minimal change disease in children commonly affects males but in adults the male to female ratio is equal. Mesangio proliferative lesion also shows male preponderence.In case of multiple myeloma, females are affected more than males (male:female ratio is 1:4) In this study, male female ratio for membranous nephropathy, membrano proliferative is 2:1 and 3:1 respectively. In case of amyloidosis male: female ratio is equal in this study. In other types of lesion, males are predominantly affected.



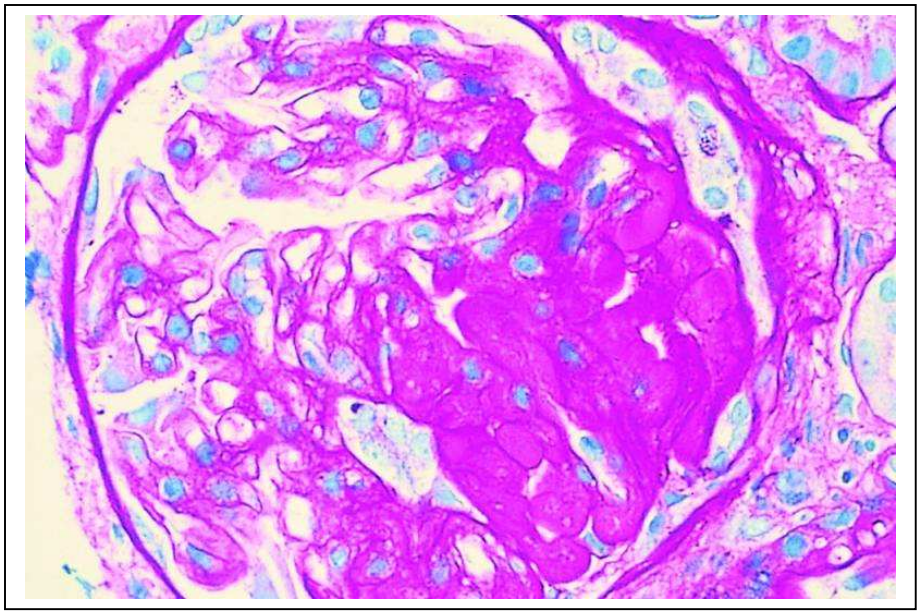
MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS (PAS STAIN)



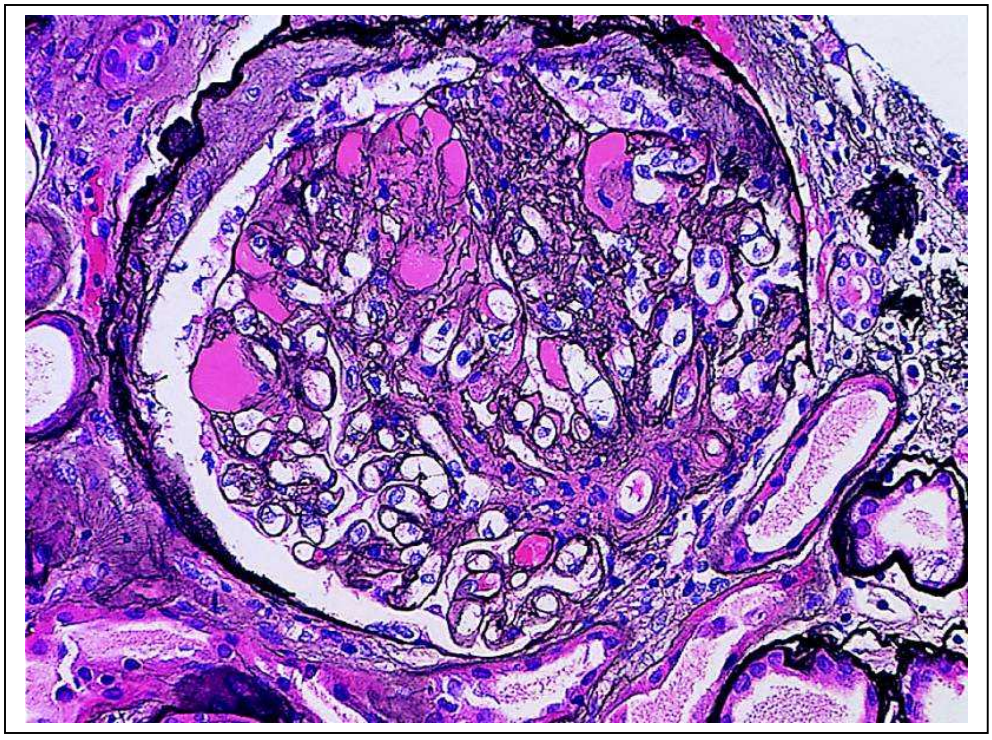
MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS – METHANAMINE SILVER STAIN



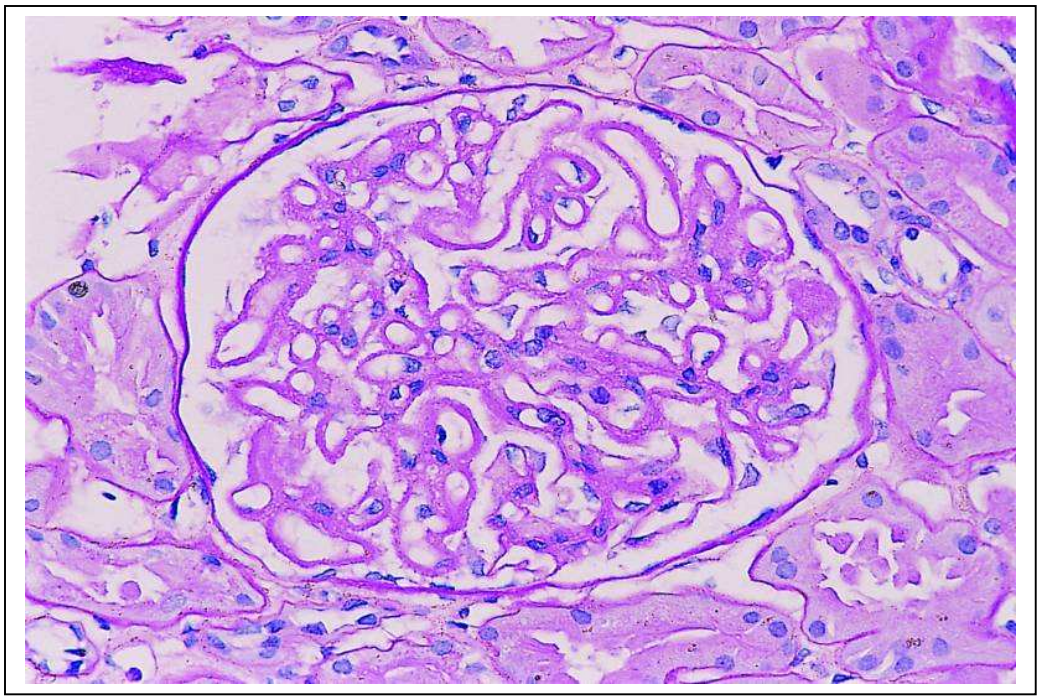
IMMUNOFLUORESCENCE OF MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS – TYPE I.



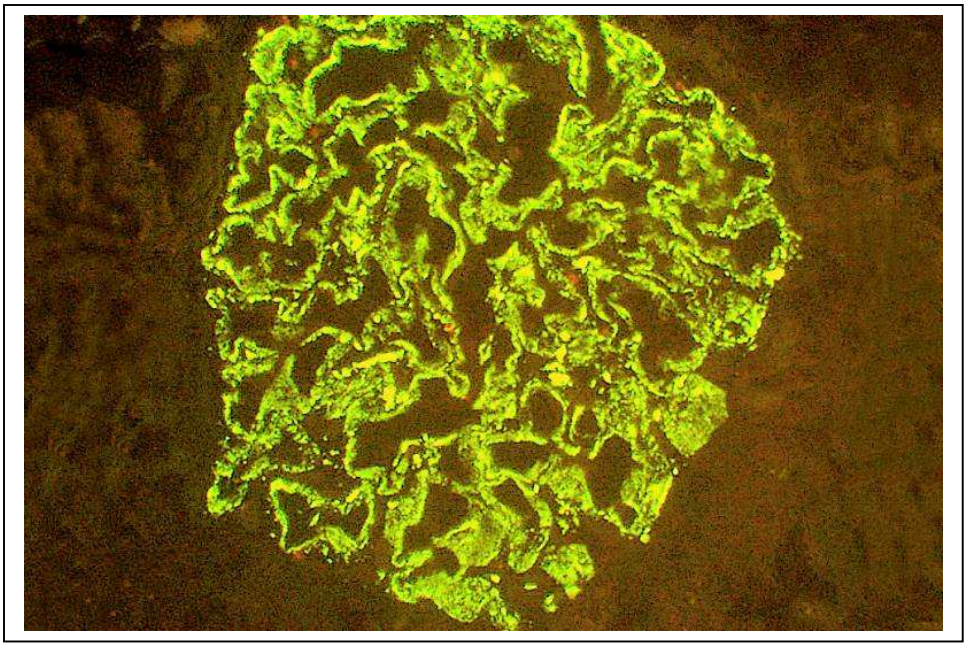
FOCAL SEGMENTAL GLOMERULOSCLEROSIS – TYPICAL LESION.



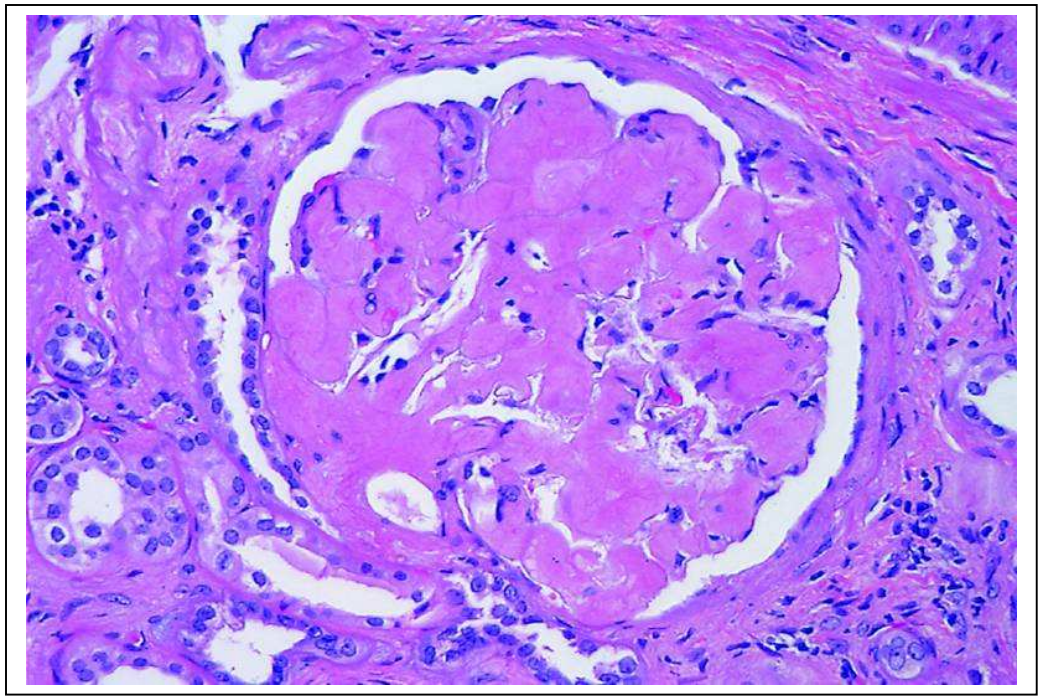
FOCAL SEGMENTAL GLOMERULOSCLEROSIS –METHANAMINE SILVER STAIN.



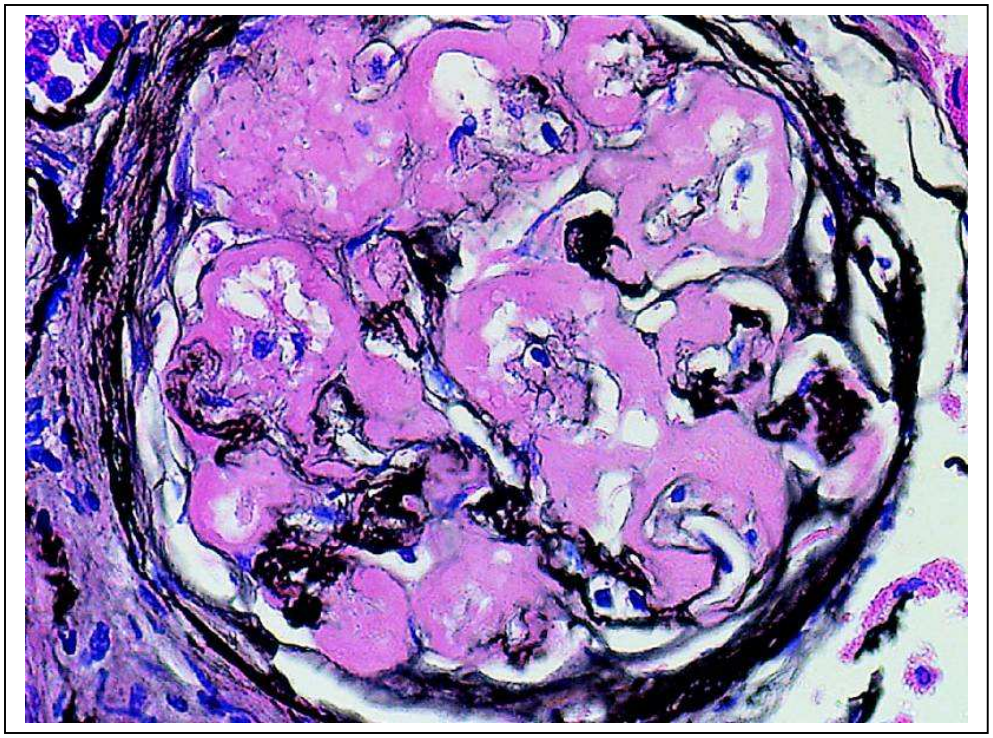
MEMBRANOUS GLOMERULONEPHRITIS – PAS STAIN.



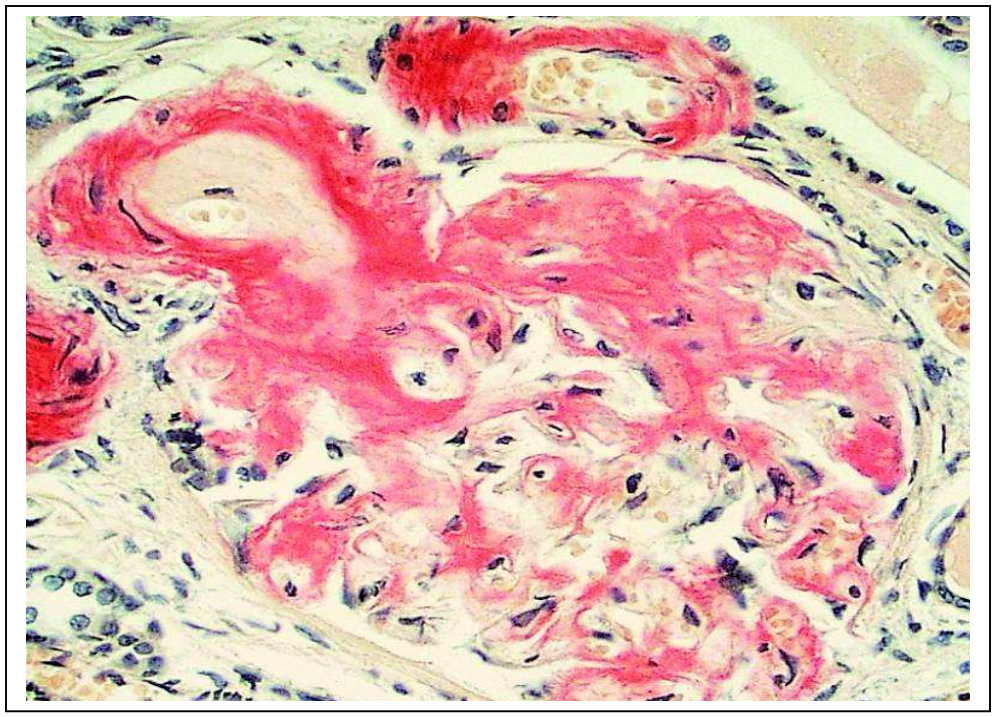
IMMUNOFLUORESCENCE OF GLOMERULUS IN MEMBRANOUS GLOMERULONEPHRITIS.



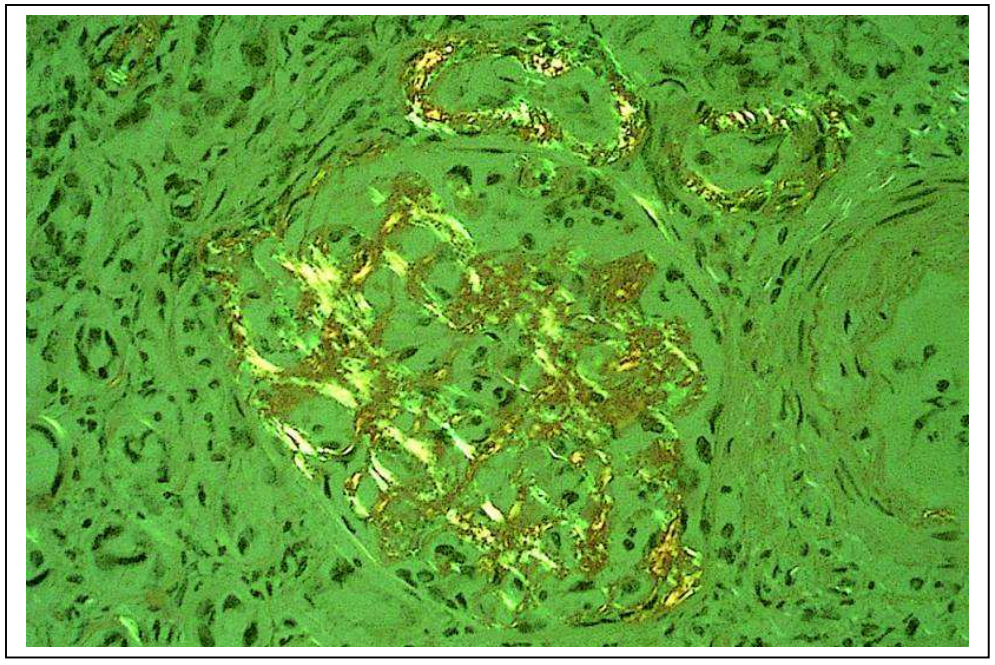
RENAL AMYLOIDOSIS



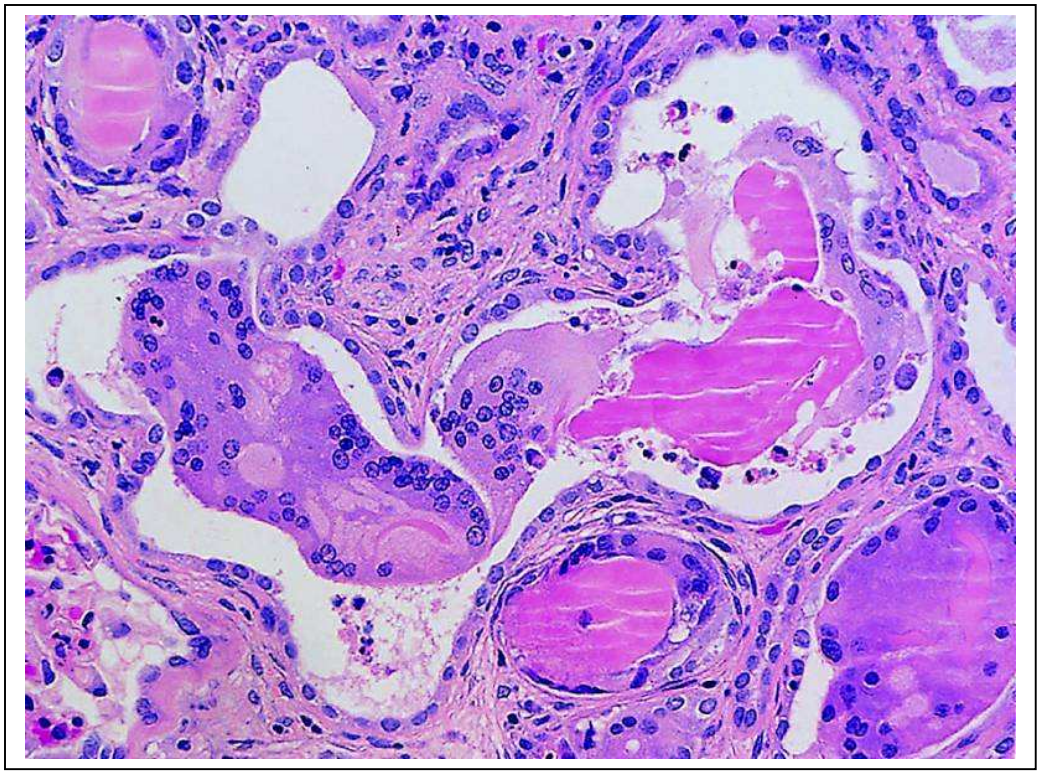
RENAL AMYLOIDOSIS - METHANAMINE SILVER STAIN



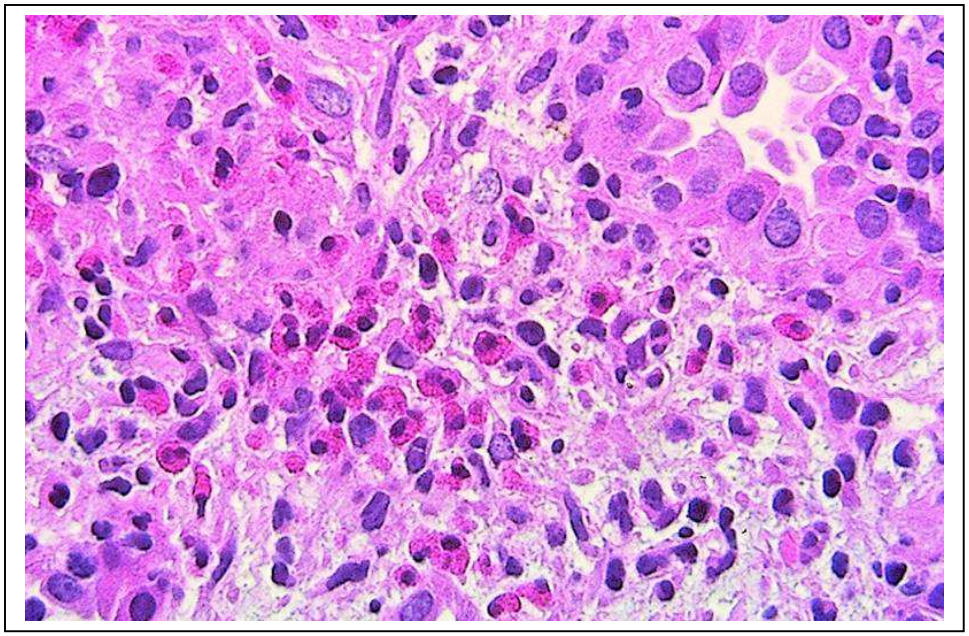
RENAL AMYLOIDOSIS – CONGO RED POSITIVE AMYLOID DEPOSITS



RENAL AMYLOIDOSIS – APPLE GREEN BIREFRINGENCE OF CONGO RED POSITIVE AMYLOID MATERIAL IN A GLOMERULUS UNDER POLARISED LIGHT.



MYELOMA CAST NEPHROPATHY.



DRUG INDUCED ACUTE INTERSTITIAL NEPHRITIS.

Clinical features:

Kark et al says that in the nephrotic syndrome almost all patients will present with anasarca, the onset being gradual. In this study, it was observed that anasarca occurred in 100% of cases, ascites in 32% of cases, hypertension in 32% of cases, and oliguria in 56% of cases. Since we found significant hypoproteinemia in all the cases, we attributed the massive edema secondary to proteinuria, though other factors also played a part in its production. In Shanbag's series, all of them had massive edema. [49] Sharma et al also reported massive edema in the majority of the cases. Mukherjee reported 18% of his patients had ascites in his series. [50]

Hypertension is seen in about a third of the patients. Cameron et al described hypertension as a frequent finding. West found that patients often had hypertension when they first presented, then it would subside and reappear years later when they develop chronic renal failure. In addition, in elderly we cannot be certain about the renal cause of hypertension in a particular case because the hypertension may be due to superimposed essential hypertension as stated by Cameron.

Though the blood volume and plasma volume are usually within normal limits, de wardener noted that the blood volume markedly changes when the patient assumes an upright position after lying in supine position for sometime and hence the patient may suffer from orthostatic hypotension. This study did not reveal any postural hypotension.

Proteinuria:

The various reports by different authors suggest that the amount of proteinuria has no role in identifying particular type of lesion since any amount of protein may be lost in any lesion. Hardwicke and Squire developed the concept of selectivity of proteinuria from the observation that proteins of different molecular weight are excreted in the urine in differing quantities in various histological forms of nephrotic syndrome. Selectivity index is the ratio of the clearance of individual proteins to the clearance of a reference protein such as albumin or transferrin. If the value is less than 0.1 it is highly selective, moderately selective if it is between 0.11 to 0.20 and poorly selective if its is > 0.20.

This study shows that proteinuria in cases of membranous nephropathy, membranoproliferative and mesangioproliferative lesions as 3.31 to 4.66 gm, 3.20 to 5.59 gm, 3.80 to 4.25 gm of protein excretion in 24hours respectively. In case of chronic glomenulonephritis 4.2 gm, acute interstitial nephritis 6.73 gm, multiple myeloma 6.8 gm, amyloidosis 3.78gm and in focal segmental glomonulosclerosis as 3.86 gm per 24 hours.

Proteinuria by various authors in various types of lesion is reported as follows. 5.98 per 24 hrs (Shanbag) 4.5 gm/24 hrs (Mukherjee) in minimal lesion, 7.1 gm/24 hrs (Mukherjee) 6.6 gm/24 hrs (Shanbag) in membranous lesion, 6.4 gm/24 hrs (Mukherjee) 5.5 gm / 24 hrs (Shanbag) in membrano proliferative lesion, 5.9 gm/24 hrs (Shanbag) 5.7 gm/24 hrs (Mukherjee) in mesangio proliferative lesion. Shanbag reported 6.2 gm/24 hrs in sclerosing lesion. Thus the various report suggest that the amount of proteinuria has no role in identifying particular type of lesion, since any amount of protein may be lost in any lesion.

Haematuria:

The precise origin of red blood cells in the urine in glomerular disease is not well known. They gain access to Bowman's space by passing through the occasional rents or tears in the glomerular capillary wall. Red cells may also enter the urine via extra vasation from the peritubular capillaries. When red cells are present in the tubular lumen proximal to the site of Tamm-Horsfall secretion, they may be incorporated into a matrix composed of Tamm-Horsfall protein to produce red cell casts. Heyman showed that red cells in the urine of nephrotics are usually intact in contrast to many lysed cells found in the smoky brown urine of patients with acute nephritis. In this study, microscopic hematuria is found in 36% of cases, most of the membranous nephropathy type and also in membranoproliferative and chronic glomenulonephritis.

Serum protein:

Serum protein levels are depressed below normal in most of the patients with massive proteinuria. There is an approximate correlation between the degree of proteinuria and the extent of hypoproteinemia. Mallick et al, Heyman W et al, Newmark S.R. et al, Kahnna UB et al and Katiyar et al found a negative correlation between serum protein and cholesterol. In this series all patients were having a low serum protein and a high cholesterol value. Hypoproteinemia may be due to urinary loss, increased protein catabolism and decreased protein synthesis. Existence of an intestinal loss of proteins and poor protein intake were also explained.

Serum cholesterol:

Hyperlipidemia forms an important component of nephrotic syndrome. The reduced plasma oncotic pressure from hypoproteinemia results in enhanced hepatic production and interferes with their peripheral utilization and catabolism. Khanna UB et al showed that there was a positive correlation between the degree of proteinuria and hyperlipidemia and a negative correlation between hypoproteinemia and hyperlipidemia. Mallick et al and new Mark SR et al also observed the same finding. In this study, all patients are having hypercholesterolemia.

However the western studies differ from this series in an important aspect. The average values in this study were lower than those observed by the western authors. This difference in the lipid pattern could be due to different dietetic pattern of our people as regards to the carbohydrate and fat content of the diet.

Histopathological correlation:

Membranous lesion:

44% of patients of this study belonged to this histopathological group. Other reported it to be 44% (Moorthy and Zimmerman, 1980), 37% (Ishimuto et al, 1981) 69% (Lustig et al, 1982) 52% (Zech et al, 1982), 50% (Kingwood et al, 1984), 33% (Murphy et al, 1987) 50% (Sato et al, 1987), 66% (Johnston et al, 1992) 65% (Ozono et al, 1994), 48% (Shin et al, 2001), 38% (Brown). [21,30-39] Membranous glomerulopathy was found to be the commonest histopathological lesion in elderly nephrotics. Membranous nephropathy in this study accounted for 11 out of 25 cases. In this study, the disease was insidious in onset and all the patients presented with anasarca. 50% of patients with membranous nephropathy presented with scanty mictuirition. 4 patients (40%) had ascites and 3 patients (30%) had hypertension. Microscopic haematuria was found in 54% of patients with this histological type.

Membranoproliferative lesion:

4 out of 25 cases in this study (16%) showed evidence of membranoproliferative glomerulonephritis. The other reports are 11% (Fawcett et al, 1971) 50% (Huriet et al, 1975), 6% (Moorthy and Zimmerman, 1980) 12% (Ishimuto et al, 1981), 8% (Lustig et al, 1982), 6% (Zech et al, 1982) 9% (Kingswood et al, 1984) 33% (Murphy et al, 1987), 12% (Sato et al 1987), 20% (Ozono et al, 1992), 14% (Shin et al, 2001), 7% (Brown). [21,28-38] Huriet et al showed this type was the commonest lesion in his study. This lesion is gaining importance in a transplanted kidney and associated with low C_3 complement and also called as Hypocomplementemic nephritis (or) Type II membranoproliferative glomerulonephritis. All the patients presented with anasarca and 75% of them had ascites, 50% of the patients presented with scanty mictuirition. One out of 4 patients had hypertension. 2 patients had microscopic hematuria. Brunner stated that 25-30% of patients presented with acute nephritic syndrome. This study showed 25% of patients with this histological type were having azotemia.

Mesangioproliferative lesion:

16% of patients of this study belonged to this group. The other reports are 20% (Moorthy and Zimmerman 1980), 3% (Zech et al, 1982), 34% (Kingwood et al, 1984), 21% (Sato et al 1987), 10% (Johnston et al, 1992). [30,33,34,36,37] In this study, the disease was insidious in onset and all the patients presented with anasarca and 75% of the patients presented with scanty mictuirition and ascites was present in 1 patient (25%). All patients had hypertenion. Asymptomatic haematuria with or without proteinuria is a common clinical feature of this lesion but this study showed no haematuria. Azotemia was present in 1 patient (25%). Johny KV stated that acute anuria at the onset and its persistence for over 3 weeks often indicates extracapillary form of glomerulonephritis and poor prognosis. On clinical grounds alone, it is difficult to separate this goup of patients from those with minimal change disease.

Focal segmental glomerulosclerosis:

One patient in this study showed evidence of focal segmental glomerulo sclerosis (4%). In other studies it was 44% (Fawcett et al, 1971), 3% (Moorthy and Zimmerman, 1980), 50% (Ishimuto et al 1981), 3% (Johnston et al 1992). [28,30,31,37] Fawcett et al and Ishimutto et al showed that it was the commonest lesion in their study. This patient presented with anasarca, proteinuria, hypoalbuminemia, hypercholesterolemia, but not with hypertension, azotemia or haematuria.

Chronic glomerulanephritis:

One case in this study (4%) belonged to chronic glomerulonephritis. Fawcett et al [28] in his study of 36 cases of elderly nephrotic syndrome reported 5 cases (13%). Zech et al [33] reported as 5%, and Shin et al [39] reported chronic glomerulonephritis as a cause of elderly nephrotic syndrome in 0.5% of cases in his study. This patient presented with insidious onset of anasarca, scanty mictuirition and microscopic haematuria but normotensive and was not having azotemia.

Acute interstitial nephritis:

One patient of this study 4% showed evidence of acute interstitial nephritis and one case of membrano prolifertive nephritis also showed superimposed interstitial nephritis (Case no. 24). In this study, this patient presented with anasarca and scanty mictuiration without haematuria or azotemia.

Native drug:

A single case of nephrotic syndrome following native drug ingestion was noted in this study. Native drugs usually contain heavy metals like mercury, lead, arsenic etc. in powder form. It is a well known fact that these drugs can cause nephrotic syndrome by its nephrotoxicity. Our case presented after a week of ingestion of the drug.

Though there is a possibility of independent primary glomerular disease causing nephrotic syndrome in this patient, because of ingesion of native drug we attributed the cause of nephrotic syndrome to the native drug, which must have had the heavy metal. There are some case reports in the literature by various authors (Brown, Munch and Nissen, Preedy and Ruissel, Riddle, Heptinstall). The case report of Samitz et al is interesting because he was the first person who explained that the nephrotic syndrome can occur due to a definite allergy to the heavy metal affecting glomeruli rather than due to its toxic effect on proximal convoluted tubule. Beckar et al reported 6 cases of this type and came to the conclusion that the onset of membranous glomeralonephritis frequently followed an immunologic event. Barr et al reported minimal lesions on light microscopy. Our case showed acute interstitial nephritis type lesion on light microscopy.

Multiple myeloma:

One case of this study (4%) belonged to this group. In this study, this patient presented with anasarca, hypercholesterolemia and azotemia but was not hypertensive and showed no haematuria. In various studies done by Confalonieri R. et al [41] (1988), Ganeval D. et al [43] (1984), Buxbaum J.N. et al [42] (1990), Heilman R.L. et al [44] (1992) and Lin et al [45] (2001), multiple myeloma presented with haematuria in 45% of cases, azotemia in 90% of cases.

58% of patients were hypertensive and 23-67% of multiple myeloma patients had nephrotic range of proteinuria. High prevalence, early appearance and severe renal failure are other salient features of Monoclonal immunoglobulin deposition disease. (Randal et al 1976, Tubbs et al 1981, Lin et al 2001 and Ronco et al 2001) [45-48]

Amyloidosis:

Two cases of amyloidosis (81%) secondary to tuberculosis is noted in this study. In thirty percent of elderly patient in medical Research Council Glomerulo nephritis Registry from 1978 to 1990, biopsied for nephrotic syndrome that showed renal amyloidosis in 10.7% of cases. Other reports are S. Prakash (22.8%), Dixon (14%), Shanbag (10.4%), Brown [21] (15%) and Johny (2.1%) Mittel et al studied 29 cases of renal amyloidosis, out of which 20 cases were due to tuberculosis. Lampa S et al reported 3 cases out of 12 cases of nephrotic syndrome.

There are so many single case reports from various parts of our country. Sarin has brought to light that amyloidosis is not a rare disease in our country and this has been more recently supported because of the availability of sophisticated techniques by other workers like Chugh et al, Mathur and Srinivasan, Tyagi and Wagi. They put the incidence at nearly 27% in all renal biopsy specimens.

The frequency of amyloidosis at large or even in all populations with a high risk is not known. Most of the available information has been on the antemortum or postmortum prevalence study of few of the selected population. (Patients known to have leprosy, TB so forth) In western literature, there is a general agreement that the apparent incidence of secondary amyloidosis is decreasing, while there is an increase in primary amyloidosis. The increase in incidence of primary amyloidosis reflects an increased awareness and better diagnostic tools, whereas the decrease in secondary amyloidosis may be due to earlier detection of cases and immediate treatment of causes. This can be easily evident from the reports of Kayle and Bayrd in 1975 who reported absence of secondary amyloidosis due to tuberculosis, whereas Dixon in 1968 has reported the incidence of 14% due to tuberculosis.

The interesting controversial phenomenon centering on amyloidosis is the correlation between it and blood pressure. Hypertension was noted to be frequent in the 42 patients described by Brandt, Catchcart and Cohen but, in contrast to this, Heptinstall and Joekas found normal pressure in their cases, as noted in this study. Bentwich, Roseman, and Eliakins (1971) in a special investigation into the prevalence of hypertension in renal amyloidosis, found it to be present in 20% of a series of 50 patients.

They came to a conclusion after careful studies of cases of amyloidosis that hypertension results with very extensive renal involvement and with vessel wall deposits producing intimal fibrosis and cystic medial hypertrophy.

Analysis of the patients with various histological appearance will reveal the fact that unlike clinical syndromes which have a quite variable prognosis, the histological data provide on excellent guide to the outcome of the patient. Three major histological patterns were observed by Cameron and Chugh et al.

1. In patients with normal or nearly normal looking glomeruli acute exudative lesions, proliferation confined to the mesangium and focal proliferative disorders without systemic vasculitis, death from renal failure was unusual.
2. When there is obvious structural damage with scarring such as membranous nephropathy, focal segemental sclerosis, proliferative glomerulonephritis and membranoproliferative glomerulonephritis, there is a steady progressive mortality.
3. Patients with extensive crescent formation as well as glomerular proliferation do very badly with a fulminant course.

Comparison of histopathological lesions with various studies

Histopathological lesion	Fawcett et al (1971)	Moorthy and Zimmerman (1980)	Ishimuto et al (1981)	Zech et al (1982)	Johnston et al (1982)	Kingswood et al (1984)	Brown (1986)	Sato et al (1987)	Shin et al (2001)	This study
Minimal change	17	27	7	33	21	7	18	13	26	-
Membranous	14	44	37	52	66	50	38	50	48	44
Membrano proliferative	11	6	12	7	-	9	7	14	14	16
Mesangio proliferative	-	20	-	3	10	34	6	21	-	16
Glomerulo sclerosis	44	3	44	-	3	-	-	2	11.5	4
Chronic glomerulo nephritis	14	-	-	5	-	-	-	-	0.5	4
Amyloidosis	-	-	-	-	-	-	15	-	-	8
Multiple myeloma	-	-	-	-	-	-	-	-	-	4
Other	-	-	-	-	-	-	17	-	-	4

CONCLUSION

CONCLUSION

A study of clinical features, biochemical changes and histopathological examination of renal biopsy specimens was done in 25 patients with nephrotic syndrome admitted in Thanjavur Medical College Hospital between December 2003 to July 2005.

1. The maximum incidence occurred in the sixth decade of life.
2. The male to female ratio is 7:3.
3. The most common cause of nephrotic syndrome was found to be primary glomerular disease (80%). Membranous glomerulopathy was the commonest histopathological lesion.
4. Some rare cases of nephrotic syndrome due to amyloidosis, multiple myeloma, drug toxicity were also noted.
5. Presence of hypertension, hematuria, azotaemia correlated with membranous gromerulopathy, membranoproliferative and mesangioproliferative, multiple myeloma and amyloidosis.
6. Hypertension, azotemia and hypercholesterolemia were observed in 32%, 32% and 100% respectively. This suggests that hypertension and azotemia are not uncommon in nephrotic syndrome.

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PROFORMA

CLINICOPATHOLOGICAL CORRELATION OF NEPHROTIC SYNDROME IN ELDERLY PATIENTS

PROFORMA

Name:	Age:	Sex:
Address:	DOA:	DOD:
I.P. No.:		

Presenting Symptoms:

Puffiness of face	Abdominal distention
Swelling of legs	Bone pain
Oliguria	Headache
Haematuria	Others

Previous Illness

Hypertension	Diabetes mellitus
Drug intake	Native medicine intake
Previous renal disease	

Personal History

Smoking	Alcohol intake

General Examination

Height	Weight	Pulse
Anemia	Skin lesion	BP

Facial puffiness	JVP
Pedal Odema	
CVS :	Abd :
RS :	CNS :
	Fundus :

Investigations

Urine	Albumin		
	Sugar		
	Deposit		
	24hrs urine protein		
	Culture and sensitivity		
	Bence Jones protein		
Blood:	Hb	Sugar	St. protein
	TC	Urea	Albumin
	DC	Creatinine	Globulin
	CT		
	RBC	St. Cholesterol	
	ESR		

- USG Abdomen X-ray – KUB

- Renal Biopsy: Date :
  No. :
  HPE Report :

Remarks:

MASTER CHART

Sl. No.	Name	I.P. No.	Age	Sex	Presenting Symptoms	Duration of illness	Blood Pressure mmHg	24hrs Urine Protein gms	Urine deposits RBC	Blood. Sugar mg%	Blood. Urea mg%	Serum creatine mg%	Serum Cholesterol mg%	Total Serum Protein gm%	Serum electrolytes		Histopathological lesion
															Na^+	K^+	
1	Gurunathan	782566	65	M	Anasarca, Ascites	1 month	130/80	3.31	4-6 RBCS	92	28	1.0	372	4.5	138	4.5	Membranous nephropathy
2	Alamelu	784901	60	F	Anasarca, Ascites	5 months	150/96	3.82	No RBCs	112	74	2.4	318	5.2	138	4.7	Membranous nephropathy
3	Ponnusamy	785608	66	M	Anasarca	2 months	120/80	3.77	4-6 RBCs	88	40	1.2	287	5.6	140	3.8	Membranous nephropathy
4	Sourirajan	786289	59	M	Anasarca, Scanty mictuirition, Ascites	1 month	160/100	4.2	No RBCs	110	70	2.8	320	4.8	136	4.1	Membranous nephropathy
5	Chinnaiyan	787346	55	M	Anasarca	1 month	130/80	3.89	7-9 RBCs	98	80	3.8	234	4.6	136	3.8	Membranous nephropathy
6	Ali	788426	53	M	Anasarca,scanty mictuirition, Ascites	2 months	130/80	5.59	No RBCs	106	24	0.8	286	5.7	137	4.6	Membrano proliferative Glomarulonephritis
7	Jeganathan	789641	55	M	Bone pain, Anasarca	1 month	120/80	6.8	No RBCs	87	92	3.8	248	5.5	132	5.2	Multiple mycloma
8	Suryaraja	789692	51	M	Anasarca, Ascites	2 months	120/80	3.2	4-6 RBCS	88	80	3.8	282	4.9	133	3.8	Membrano proliferative Glomarulonephritis
9	Chandra	796021	55	F	Anasarca, Scanty mictuirition	15 days	160/100	4.66	No RBCs	90	32	3.8	240	4.8	136	3.6	Membranous nephropathy
10	Pandian	797162	55	M	Anasarca, Scanty mictuirition	1 weeks	120/70	6.73	No RBCs	108	32	3.8	294	5.7	136	4.4	Acute interstitial nephritis
11	Premavathy	811926	55	F	Anasarca, Asistes	2 months	110/70	4.2	3-5 RBCs	86	30	0.9	320	5.2	138	3.9	Membranous nephropathy
12	Muruganantham	812843	63	M	Anasarca, Scanty mictuirition	3 months	126/80	3.67	8-10 RBCs	110	32	1.0	290	4.4	136	4.1	Membranous nephropathy

Sl. No.	Name	I.P. No.	Age	Sex	Presenting Symptoms	Duration of illness	Blood Pressure mmHg	24hrs Urine Protein gms	Urine deposits RBC	Blood. Sugar mg%	Blood. Urea mg%	Serum creatinine mg%	Serum Cholesterol mg%	Total Serum Protein gm%	Serum electrolytes		Histopathological lesion
															Na^+	K^+	
13	Selvamani	813061	52	M	Anasarca	1 month	110/74	3.62	No RBCs	110	30	0.8	296	5.7	140	3.8	Membranous nephropathy
14	Neelamangalam	815628	56	M	Anasarca	1 month	170/110	4.2	No RBCs	108	94	3.4	420	4.9	138	4.4	Mesangio proliferative glomerulonephritis
15	Saraswathy	817281	54	F	Anasarca, Scanty mictuirition	3 months	120/80	4.2	4-6 RBCS	110	30	1.0	380	4.8	134	4.2	Chronic glomenlo nephritis
16	S. Renganathan	820721	70	M	Anasarca, Scanty mictuirition	4 months	130/80	3.37	No RBCs	126	96	2.8	320	5.6	140	4.1	Amyloidosis
17	Natesan	822814	55	M	Anasarca, Scanty mictuirition	2 months	120/80	3.8	4-6 RBCS	120	30	1.0	246	5.2	136	3.8	Membranous nephropathy
18	Alamelu	823421	65	F	Anasarca, Scanty mictuirition	3 months	120/80	4.2	No RBCs	106	30	1.1	280	5.6	136	4.2	Amyloidosis
19	Vellaiyammal	824823	55	F	Anasarca	1 month	120/80	3.86	No RBCs	112	28	0.8	256	5.6	137	4.1	Focal Segmental Glomerulosclerosis
20	Marimuthu	825210	53	M	Anasarca, Scanty mictuirition	2 months	156/100	4.25	No RBCs	108	32	1.1	340	5.2	136	4.3	Mesangio proliferative glomerulonephritis
21	Subbaiyan	828421	64	M	Anasarca, Scanty mictuirition	2 months	120/80	3.8	No RBCs	98	30	0.8	260	4.98	136	4.1	Membranous nephropathy
22	Venkatachalam	830982	71	M	Anasarca, Scanty mictuirition	3 months	160/100	3.8	No RBCs	110	108	3.8	310	4.8	130	4.1	Mesangio proliferative glomerulonephritis
23	John	834814	54	M	Anasarca, Ascites	2 months	110/76	3.64	No RBCs	110	30	0.8	286	5.5	136	4.2	Membrano proliferative glomerulonephritis
24	Kanni	843612	58	F	Anasarca, Scanty mictuirition	1 month	160/90	3.2	6-8 RBCs	110	34	1.0	240	4.8	136	4.2	Membrano proliferative Glomarulonephritis
25	Ravidran	844521	52	M	Anasarca, Scanty mictuirition, Ascites	3 months	160/96	4.0	No RBCs	108	30	1.2	410	5.8	138	3.8	Mesangio proliferative glomerulonephritis